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DIAGNOSIS AND TREATMENT OF STRICTURES OF THE AQUEDUCT OF SYLVIUS (CAUSING HYDROCEPHALUS)

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Strictures of the aqueduct of Sylvius (the iter) are congenital maldevelopments, characterized by a replacement of this channel with glial tissue. Histologically remnants of this epithelial-lined channel are present (fig. 5 *A* and *B*). At times the stricture is not complete but is so tiny that fluid can pass only intermittently, or at least incompletely.[1] Occasionally a stricture of the iter may follow a healed infection within the ventricles, but with these rare exceptions the strictures are of congenital origin.

Since the aqueduct of Sylvius is the only channel for passage of the cerebrospinal fluid that arises from the choroid plexuses of the third and both lateral ventricles, hydrocephalus involving these ventricles is a necessary and unfailing sequel when this channel is closed. There are no other collateral channels through which the fluid can be sidetracked spontaneously. When the occlusion is complete, the hydrocephalus is fulminating and produces rapid destruction of the brain. If the cranial sutures are open, the head increases in size; if they are closed, but not too tightly, when the obstruction develops, they may separate and cause moderate enlargement of the head (in childhood); if they are tightly closed, no enlargement can occur. The diagnosis of hydrocephalus may therefore be exceedingly simple for infants, less so but definite for children and difficult for adults. When the head cannot enlarge, hydrocephalus can be diagnosed only by convolutional atrophy shown in the roentgenograms or by ventriculography.

Hydrocephalus results from obstructions along the cerebrospinal circulatory system in four general locations: (1) the foramens of Monro, (2) the aqueduct of Sylvius, (3) the foramens of Magendie and Luschka and (4) the cisternae along the base of the brain. Of these, obstructions of the aqueduct of Sylvius account for about half of the cases of hydrocephalus in infants. Hydrocephalus arising from congenital strictures of the aqueduct of Sylvius is infrequent after infancy, though still common enough to be considered in differential diagnosis, and particularly through childhood. After infancy, tumors are responsible for hydrocephalus in perhaps 95 per cent of the cases of hydrocephalus, and in infancy congenital occlusions account for about 95 per cent of the cases. After infancy, therefore, a tumor is the presumptive cause of hydrocephalus on the law of probability. It is for this remaining group of 5 per cent, therefore, that the diagnosis of a stricture is all-important. If the diagnosis is missed, the patient is subjected to a big cerebellar operation that is unnecessary and not without danger to life. If the diagnosis is made correctly, the treatment is simple, is relatively safe and will usually cure.

Fig. 1.—Retouched ventriculogram showing the triangular or funnel-shaped aqueduct that is characteristic of a stricture at the aqueduct.

DIAGNOSIS OF STRICTURE OF THE AQUEDUCT IN INFANTS

For infants the diagnosis of a stricture at the aqueduct is simple and fairly free from error. If the dye test (phenolsulfonphthalein) shows an obstruction in the ventricular system, the obstruction will be either at the aqueduct or at the foramens of Magendie and Luschka. And if the inion is low, the obstruction will be at the aqueduct; if the inion is high the obstruction will be at the foramens of Magendie and Luschka. The height of the inion is therefore all-important

1. Dandy, W. E., and Blackfan, K. D.: Internal Hydrocephalus, Am. J. Dis. Child. 8:406 (Dec.) 1914.

(fig. 4). The reasons for its importance are: 1. When the foramens of Magendie and Luschka are blocked, the fourth ventricle participates in the ventricular enlargement and the resulting increased volume in the posterior cranial fossa pushes the inion upward. 2. Conversely, when the aqueduct of Sylvius is occluded, the posterior fossa does not enlarge and the inion remains low. As a matter of fact, the inion may be, and usually

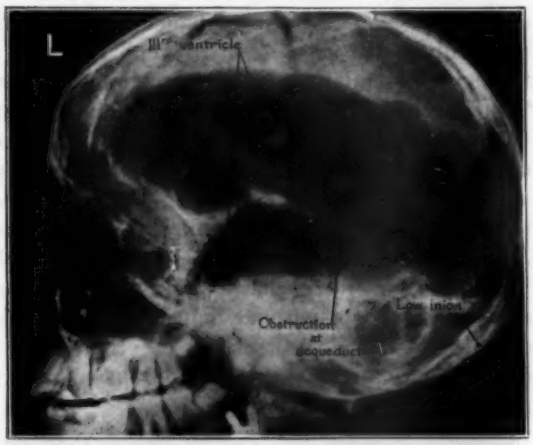

Fig. 2.—Retouched ventriculogram.

is, lower than normal because the supratentorial pressure from the greatly enlarged lateral ventricles compresses the posterior cranial fossa and therefore lowers the inion (fig. 4). This is one of the most important signs in neurologic diagnosis and localization and is no less important for children than for infants. After childhood, it has but little importance.

For localization of the lesion causing hydrocephalus in infants, therefore, ventriculography is not necessary and should not be used. If the dye passes from the spinal canal into the lateral ventricles, the ventricles are not obstructed; the cerebrospinal spaces are then blocked in the cisternae (communicating hydrocephalus), and an entirely different treatment is indicated.

DIAGNOSIS OF STRICTURE OF THE AQUEDUCT IN CHILDREN AND ADULTS

Until recently, the diagnosis of stricture of the aqueduct could be made only at operation. In children the most common lesion causing intracranial pressure is a tumor, and about two thirds of these tumors are in the cerebellum. If there are cerebellar signs, the diagnosis and localization require no further diagnostic aids. But many cerebellar tumors give no signs of localization. It is from this group that strictures of the aqueduct must be differentiated, for few, if any, localizing symptoms usually result from strictures; occasionally there is a little staggering or ataxia. Ventriculography is then necessary, and it will always accurately localize the obstruction. When this is in the anterior part of the fourth ventricle, the aqueduct and part of the fourth ventricle will be filled. A stricture can therefore be excluded. But when the air shadow shows the obstruction to be at the aqueduct, occlusion may still be due to a tumor but there may also be a stricture. Patients with this ventriculographic finding have routinely had cerebellar operations, since tumors are the probable lesions. And when tumors did not present on the surface, the exploration was carried up the fourth ventricle until the ventricular block was disclosed; at times a stricture of the aqueduct was found. When the lesion is a stricture, the conditions observed in the posterior cranial fossa are usually sufficiently normal to exclude a tumor: i. e. the cerebellar volume is not increased, the tonsils of the cerebellum are not pushed into the spinal canal (as by a tumor) and the cisterna magna is of fair size. To an experienced operator these negative findings are usually enough to make it unnecessary to carry the inspection to the aqueduct and are adequate to exclude a tumor and make the diagnosis of a stricture. With rare exceptions, when a thin diaphragm causes the block and can be opened, nothing can be done surgically to open the dense

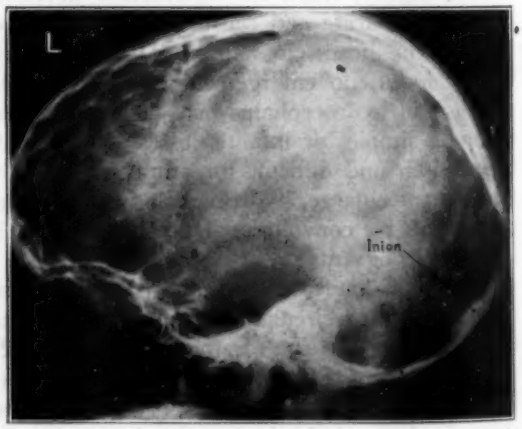

Fig. 3.—Plain roentgenogram showing convolutional atrophy, a large sella turcica and a low inion, which are so characteristic of a stricture at the aqueduct that ventriculography is scarcely necessary.

scar that usually causes the stricture. The operation therefore has done nothing but make the diagnosis and is, of course, a big and serious procedure—and certainly one to be avoided if possible.

VENTRICULOGRAPHIC DIAGNOSIS OF STRICTURE OF THE AQUEDUCT

The positive diagnosis of a stricture can now usually (not always) be made by a study of the shape of the air shadow at the obstruction as disclosed by ventriculography. The ventricular system ahead of the obstruction must be completely filled with air to insure filling of the third ventricle and of the aqueduct if it is patent. Less than complete filling leads to uncertainty and frequently to error in interpretation. The air shadow is frequently pathognomonic of a stricture. From a somewhat dilated, or possibly normal-sized, opening of the aqueduct in the third ventricle, the air shadow tapers backward to a point in the midbrain—i. e., the shadow is funnel shaped or triangular (figs. 1 and 2). The shape of the shadow is determined, of course, by the character of the lesion, i. e., a scar which gradually becomes more intense as it passes backward. Usually when this lesion is present, the entire length of the open aqueduct is less than 0.5 cm. Such a shadow differs from that of an obstruction by a tumor in that the latter causes a sudden obstruction and therefore a sharp vertical line at the point of obstruction and the part of the aqueduct anterior to it is uniformly dilated, because there is no scar to constrict it. Occasionally a diaphragmatic obstruction of the aqueduct exists, and when this obtains the roentgenographic shadow is precisely like that of a tumor; such an obstruction, however, is uncommon. It will be understood, of course, that a stricture of the aqueduct always dilates the entire ventricular system ahead of the aqueduct, and it is then necessary only to concentrate the inspection of the ventricular shadows to the point of obstruction. It will also be observed that the hydrocephalus due to a stricture of the iter is frequently much greater than that caused by tumors in the posterior fossa, because in the latter the obstruction is intermittent and of ball valve character until the final stages. It is probable that for years after birth there is a tiny lumen in an aqueduct with a stricture and that eventually it closes completely. That is the only plausible explanation for the appearance of the strictures in late childhood and even beyond.

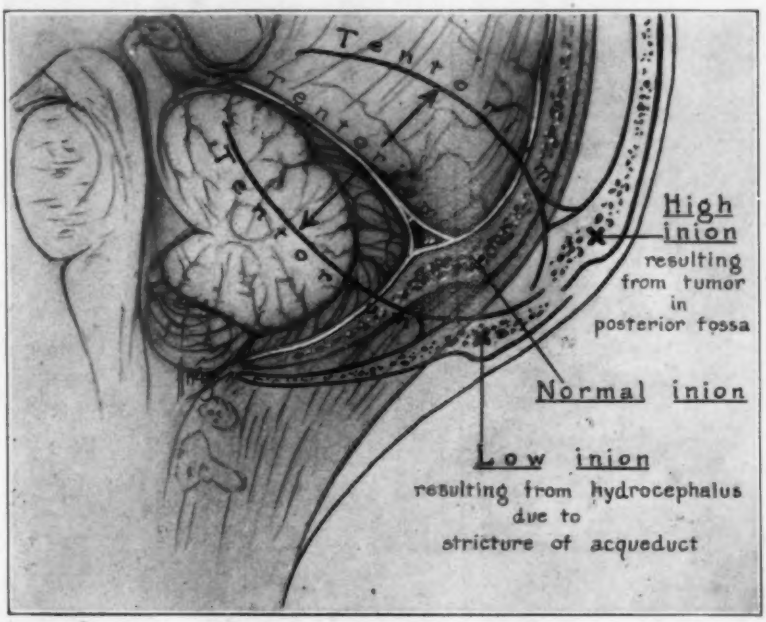

Fig. 4.—Diagram to show the shifting of the height of the inion (1) upward, by a tumor in the posterior fossa, and (2) downward, by a supratentorial pressure of hydrocephalus.

However, in none of the patients who have been operated on in this hospital has any air been found beyond the aqueduct; i. e., the strictures were then probably complete.

DIAGNOSIS OF STRICTURES OF THE AQUEDUCT WITHOUT VENTRICULOGRAPHY, I.E., BY THE HEIGHT OF THE INION

It is now possible to make the diagnosis of stricture of the aqueduct without operation and even without ventriculography. This had been done in 5 cases. The clue to the diagnosis is the height of the inion. Roentgenologic examination is usually a better guide to the site of the inion than palpation, because the inion may be difficult to feel with accuracy. Also, the lateral venous

sinuses usually show in the roentgenogram and give additional indication of the size of the posterior cranial fossa.

The size of the posterior cranial fossa is nearly always increased in the early years of life by a tumor in this position. The inion is therefore pushed upward as an expression of the increased volume. And if the inion is not higher than normal, it usually (not always) means that there is no tumor in the posterior cranial fossa. Therefore, if the head is oversize, the sutures are separated (Macewen's sign) and there is evident hydrocephalus and, at the same time, the inion is normally placed, the diagnosis of a stricture of the aqueduct is almost assured (fig. 3). Exceptions to this are the following: 1. An occasional cerebral tumor will give similar signs and symptoms but can be easily differentiated by simply tapping both lateral ventricles to determine their size. A cerebral tumor may enlarge one lateral ventricle but not both. 2. A tumor of the third ventricle cannot be differentiated in this way, because the two ventricles are equally large. The latter diagnosis cannot be made without ventriculography, but it is disclosed at operation (ventriculostomy) by the absence of a large

Fig. 5.—*A*, photomicrograph of specimen showing remains of a single ependymal channel obliterated by gliosis at the aqueduct. (Taken from Dandy, W. H., and Blackfan, K. D.: Am. J. Dis. Child. **8**:406 [Dec.] 1914).

third ventricle. On the law of probability I prefer this occasional mistake to the injection of air in all cases in which a stricture of an aqueduct is the probable lesion.

ANATOMIC REASONS FOR THIRD VENTRICULOSTOMY

By a third ventriculostomy, fluid is short-circuited from the third ventricle to the cisterna interpeduncularis and the cisterna chiasmatis, which together form the central distributing station from which the cerebrospinal fluid is normally passed along to the cerebral subarachnoid spaces, where it is absorbed. It is absolutely essential that the opening in the third ventricle where it cannot be absorbed, to the subarachnoid spaces where it is absorbed. Fortunately, the floor is membranous and thin, thereby reducing the possibility of reclosure that obtains in cases in which the walls are thicker.

TWO TYPES OF THIRD VENTRICULOSTOMY

In 1922, I [2] proposed a third ventriculostomy in the floor of the ventricle. The attack was made anteriorly through a small supraorbital approach. The third ventricle lies just behind the optic nerves, and, since these nerves in infancy are very short and there is no space between them and the olivary eminence, it was necessary to divide an optic nerve to gain access to the

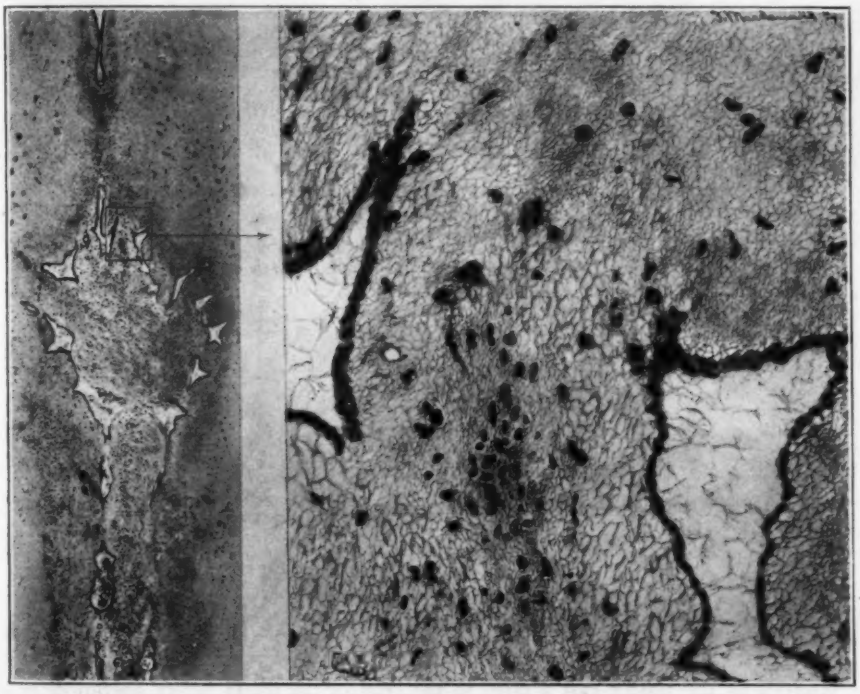

Fig. 5.—*B*, low and high power photomicrographs of a stricture of the aqueduct. In the region of the aqueduct there are numerous little cavities lined with columnar epithelium and between them a dense scar.

be made in its floor, not the roof. Nearly half a century ago the roof of the third ventricle was opened by blindly passing an instrument through the corpus callosum — the so-called *Balkenstich* procedure. An opening in the roof of the ventricle cannot cure or improve hydrocephalus, because the fluid then pours into the subdural space, where it cannot be absorbed. Moreover, the opening will not remain patent, because of subsequent cicatrization. Fluid can be absorbed only in the subarachnoid spaces. In cases of stricture of the aqueduct of Sylvius there is only one possible place—i.e., the floor of the third ventricle—from which the fluid can be side-tracked from the dilated ventricular system, third ventricle. Although there were occasional successes (and fig. 14 shows one) it was found that usually the fluid poured over the surface of the brain and an external hydrocephalus followed, i.e., the fluid poured into the subdural space, this being the path of least resistance. White (1942)[3] has continued to use this procedure, but only for adults, whose optic nerves are longer, and has reported good results. Stookey and Scarff (1936) [4] have also used this

2. Dandy, W. E.: Operative Procedure for Hydrocephalus, Bull. Johns Hopkins Hosp. **33**:189, 1922.

3. White, J. C.: Treatment of Obstructive Hydrocephalus, Surg., Gynec. & Obst. **74**:99, 1942.

4. Stookey, B., and Scarff, J.: Occlusion of the Aqueduct of Sylvius, Bull. Neurol. Inst. New York **5**:348, 1936.

approach, but instead of cutting an optic nerve they have pushed a blunt instrument backward above the optic tracts and through the posterior wall of the floor of the ventricle—certainly a hazardous attack and one that could succeed only by luck. White also tried the Torkildsen [5] attack, by which a rubber tube is passed subcutaneously from the lateral ventricle to the cisterna magna, although he also thought it difficult to believe that such a procedure, depending on permanent patency of a rubber tube and a foreign body, could ever be successful. Sweet (1940) [6] presented a necropsy specimen of a spontaneously cured hydrocephalus. There was 4 mm. opening from the anterior part of the third ventricle into the cisterna chiasmatis. It is the only demonstration of the cause of a spontaneously cured hydrocephalus.

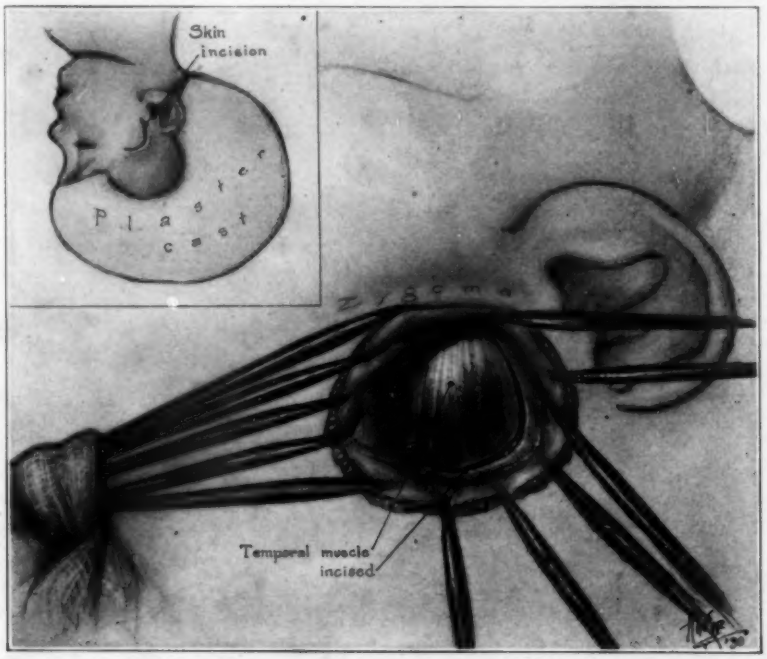

Fig. 6.—The inset shows the plaster cast applied to the head of the infant before operation, in order to prevent collapse of the head when the ventricle is opened. The site of the incision is also indicated. The main drawing shows the incision through the temporal muscle.

THE LATERAL APPROACH

An approach to the third ventricle by the temporal route was reported by me in 1932 [7] and has since been used exclusively. There are several important advantages over the frontal approach—in fact, they constitute the difference between success and failure of the third ventriculostomy in most cases. The procedure is equally applicable to infants, children and adults.

The advantages are: 1. The ventricle is opened under direct inspection—behind the infundibulum and in the cisterna interpeduncularis (not the cisterna chiasmatis), where the ventricular wall is thinnest. 2. An external hydrocephalus does not develop subsequently, because the dura lining the middle fossa of the skull ends mesially in a shelf that lies alongside the cisterna laterally. The temporal lobe falls over this shelf and prevents fluid from pouring out. The efficacy of this sealing is evident when at operation the partially collapsed lateral ventricles are filled with fluid under pressure; the fluid does not pass into the middle fossa. 3. The optic nerves are not disturbed. 4. The approach requires a smaller operative exposure and one covered by hair.

The operative attack on the floor of the third ventricle presupposes a downward bulge of the greatly enlarged third ventricle. Occasionally this does not obtain, and the procedure cannot then be carried out unless one is willing to make a blind stab for the ventricle. Such a high, nonbulging third ventricle has been encountered

5. Torkildsen, A.: A New Palliative Operation in Cases of Inoperable Occlusion of the Sylvian Aqueduct, Acta chir. Scandinav. **82**:117, 1931.

6. Sweet, W. H.: Spontaneous Cerebral Ventriculostium, Arch. Neurol. & Psychiat. **44**:532 (Sept.) 1940.

7. Dandy, W. E., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1933, vol. 12, p. 247.

twice in this series of cases, once in an infant and once in an adult. In the latter case, the anterior approach was tried subsequently, but without success. It should be noted that in children and adults the floor of the ventricle is always thicker than in infants, and, to prevent subsequent closure, a larger opening is required. In 7 cases in group I, the opening had closed after a short time, but after a second and in 1 case a third operation on the same or the other side the opening has persisted permanently.

A third ventriculostomy is also indicated in some cases of inoperable tumor of the cerebellum, in which there are no crippling sequelae of

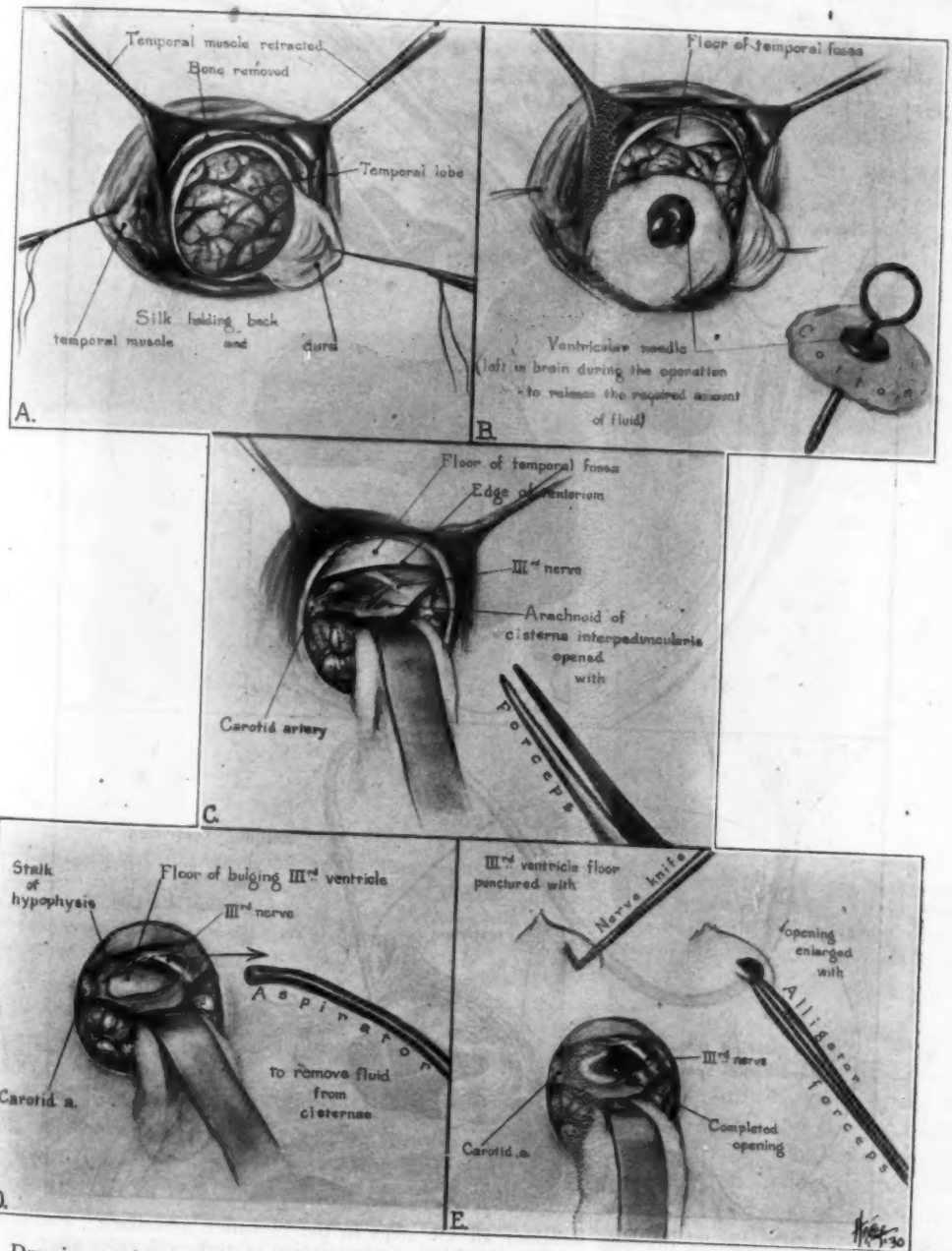

Fig. 7.—Drawing to demonstrate the steps in the procedure of third ventriculostomy by the lateral or temporal route: *A*, exposed brain. *B*, a flanged needle protected by a pledget of cotton is passed into the descending horn and left in place during the operation. Fluid rolls out in the exact amount required to gain room when the spatula elevates the temporal lobe. *C*, exposure of the cisterna interpeduncularis; the third nerve shines through the membrane. *D*, the floor of the ventricle can be seen bulging into the cisterna interpeduncularis, the wall of which is removed. *E*, opening made into the floor of the ventricle by plunging the forceps into it or by cutting it with a knife or scissors. The opening can be enlarged by spreading the forceps, by pulling the thin ventricular wall or by cutting it with angle scissors.

the tumor, such as motor paralyses or nerve palsies. It is also useful in obstructions of the foramens of Luschka and Magendie when a new foramen cannot be maintained.

forward about half this distance (fig. 6). The incision is much like that for a temporal gasserian ganglion approach but smaller and is entirely below the origin of the temporal muscle, which

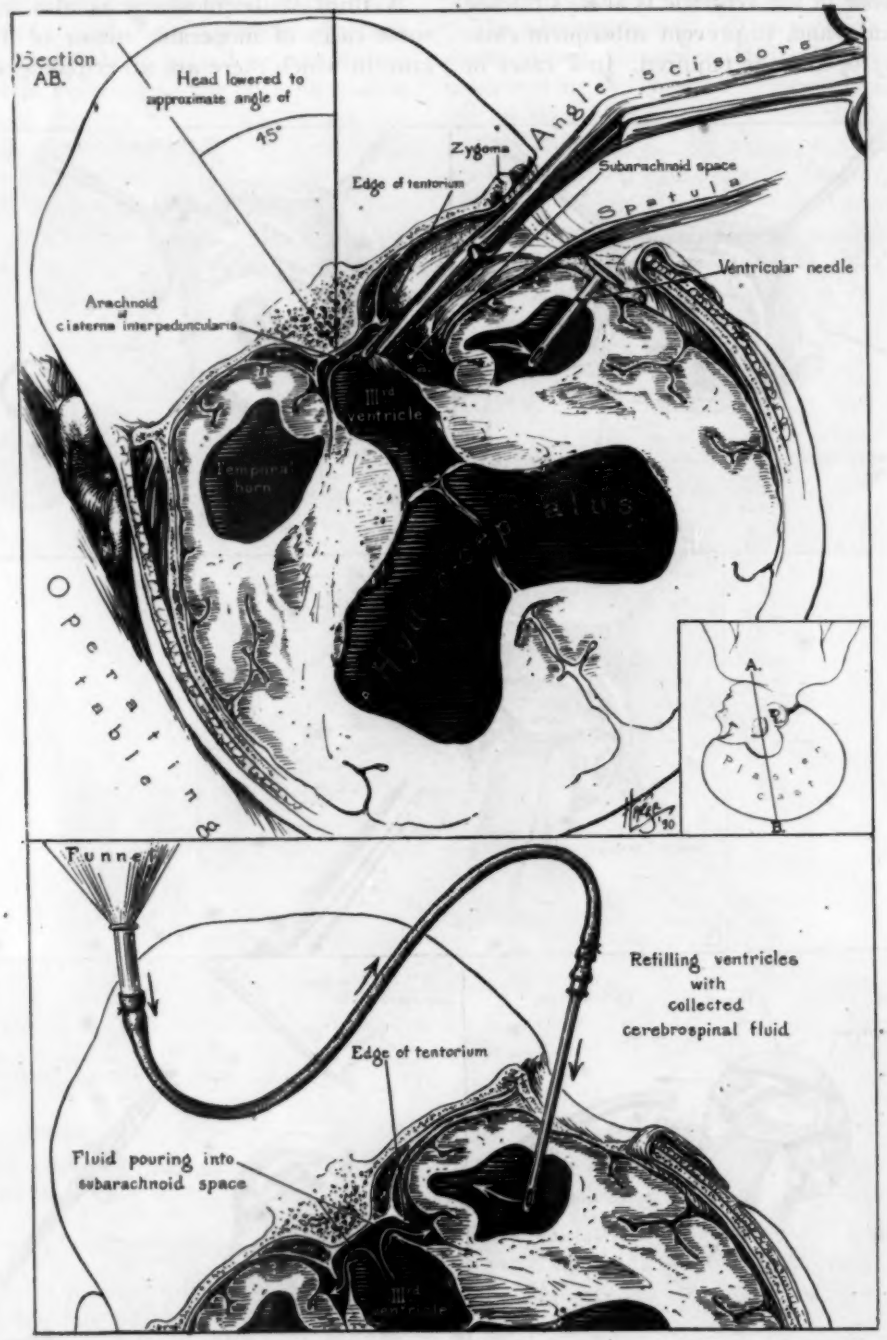

Fig. 8.—The upper composite drawing indicates all the steps in the operative procedure. The lower drawing demonstrates the method of filling the ventricles with isotonic solution of three chlorides after the operation is complete. The brain then gradually fills out until it is flush with the dura.

THE OPERATIVE PROCEDURE

A small vertical incision is made from the zygoma upward and just in front of the ear to the edge of the temporal muscle; it then curves is incised in a similar curve and retracted forward. A small circular area of bone is then rongeured away and the dura opened (fig. 7 *A*). A flanged ventricular needle is inserted into the

descending horn of the lateral ventricle and remains in place during retraction of the temporal lobe (fig. 7 *B*). The ventricular fluid is released through this needle by pressure of the spatula on the temporal lobe and in the exact amount necessary to expose the region about the third cranial nerve. The brain is therefore not subjected to severe pressure by retraction of the temporal lobe. The mesial shelf of the dura then comes into view, and a little more traction with the spatula exposes the third nerve and the thin wall of the cisterna interpeduncularis (fig. 7 *C*). The latter is incised both in front of and behind the third nerve, after which the downward bulging floor of the third ventricle is fully exposed (fig. 7 *D*). It is punctured with forceps and the opening enlarged by spreading the forceps or by cutting away the membrane (fig. 7 *E*). The newly created opening. This position is not so necessary for children and adults, but some downward declination of the head is still advisable. An infant must also have the head encased in plaster of paris (fig. 6), to prevent collapse of the brain when the ventricle is opened.

SUMMARY OF THE RESULTS IN GROUP I (OVER 1 YEAR OLD)

There are 29 patients in this group; 13 are females and 16 males. There were 5 in the first 5 years of life, 5 in the second 5 years, 15 between the ages of 10 and 20, and 4 older than 20; the oldest was 45 years. On the whole, the children in this group showed few signs and symptoms except those of intracranial pressure. Frequently the patients had had headaches throughout life, and usually these were periodic.

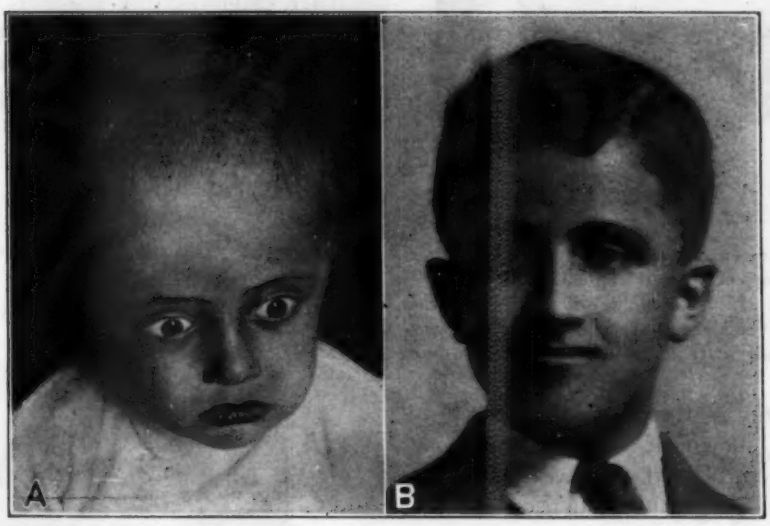

Fig. 9.—Photographs of a patient. *A*, before third ventriculostomy performed Jan. 17, 1930; he was reoperated on March 3, 1930. At that time he was 2 years old, and the circumference of the head was 62.5 cm. *B*, in 1944, fourteen years after the operation, when the patient was 16 years old. The head is now little, if any, larger than at the time of operation and is now only slightly oversize. The diagnosis of stricture of the aqueduct was made by a cerebellar exploration.

flanged needle is then withdrawn and another needle connected with a funnel is inserted in its place. Isotonic solution of three chlorides is passed by gravity into the ventricle until the brain is flush with the dura (fig. 8). The fluid emerging from the third ventricle is retained in the cisterna interpeduncularis. It is probable that external hydrocephalus will not develop so consistently following the anterior approach in the older patients because the subarachnoid spaces are open.

Infants must be placed in a head down position during the operation in order to prevent the large volume of escaping fluid from flooding the field and preventing the careful enlargement of the

The head was always oversize and usually strikingly so; the circumferences ranged from 59 to 65 cm. The cranial sutures were open, and a cracked pot sound was elicited. In many instances the sella turcica was enlarged in the anteroposterior direction owing to the pressure of the big third ventricle, and in 1 patient there were a partial bitemporal hemianopsia and complete destruction of the sella from the same cause. In every case extensive convolutional atrophy was seen in the roentgenograms—an almost pathognomonic indication of hydrocephalus.

Usually there was bilateral papilledema, at times with hemorrhages in the eyegrounds. One patient was blind and 2 others nearly so from the

intracranial pressure. In only 1 patient was there an extraocular palsy; she had bilateral ophthalmoplegia which has persisted for thirteen and one-half years after operation; doubtless the scar at the aqueduct had included the nuclei controlling the extraocular muscles. Dizzy spells were noted in 2 cases.

Fig. 10.—Photograph of a patient three years after third ventriculostomy, performed at the age of 22. The ventricles contained 275 cc. of fluid. The stricture was diagnosed by a cerebellar exploration. The baby was born two and one-half years after the mother's operation.

Ventriculography.—In all cases a complete block has been shown at the iter; in none has air been seen beyond. However, in the period before the obstruction had become total, such a finding might well have been observed. Only in recent years have the relatively high incidence of this lesion and the number of cerebellar operations in which tumors were not found led to a more careful study of the shadow at the aqueduct. It is now believed that the funnel-shaped shadow when it occurs is characteristic of the lesion. Until this fact was disclosed, 13 cases of stricture of the aqueduct had been found at cerebellar operations. Since then, 11 have been disclosed by ventriculography alone.

The size of the ventricles as measured by the amount of fluid required to fill them was 150, 180, 200, 205, 275, 300, 400, 525, 600, 650 and 720 cc. in 11 recorded cases. Particularly significant are the very large ventricles, i. e., over 500 cc. Cerebellar tumors may cause such large ventricles, but rarely do they cause ones as large as 500 cc.

DIAGNOSIS OF STRICTURES WITHOUT VENTRICULOGRAPHY

Even more gratifying is the further advance of making this diagnosis without ventriculography (in children). Even in adult life an unusually large head is carried over from childhood and may have the same significance; for 1 adult the diagnosis has been made in this way. The diagnosis is made when (1) the head is oversize; (2) there is a separation of the cranial sutures from intracranial pressure; (3) the x-rays show convolutional atrophy, and (4) most important, the inion is low, indicating the absence of a tumor in the posterior cranial fossa. The length of time the large head has been known to exist is also significant, strictures usually being of longer duration than tumors. In 5 cases the diagnosis has been made without ventriculography.

After childhood the lesion is still found but less frequently, and unless a large head indicates a carry-over from childhood the diagnosis would hardly be entertained before operation. With this exception, it is therefore always an operative disclosure in adults.

RESULTS OF TREATMENT

Group I (Over 1 year).—A total of 36 operations (ventriculostomies) were performed in the 29 cases. The reason for the 7 extra operations was that the opening in the floor of the ventricle had closed before the patient left the hospital or subsequently, and a second attempt was made either on the same or on the other side. In 6 of these cases the subsequent operation (in 1 case 2 additional operations) was successful. The presence or absence of fulness at the site of the operation (a miniature decom-

Fig. 11.—Photograph of a patient operated on at the age of 15. The ventricles contained 450 cc. of fluid. He is now 23 years old.

pression) is proof of the patency or nonpatency of the newly created opening. The decompression will be flat and soft if the hydrocephalus has been cured.

There was 1 operative death in the series. In 1 case (age 17) it was not possible to make an opening in the third ventricle because it did not descend far enough. An anterior approach was tried; the optic nerve was cut to reach it, but the opening was small and quickly closed over again. The patient died four months later. Three other patients died at home five weeks, three months and six months after leaving the hospital. In none of these cases was an autopsy obtained; one of these patients had made great improvement; in one there was no improvement, and no comment was made concerning the third. remaining patients are well, active and normal mentally and physically.

There are probably no groups of patients with a background of intracranial pressure that do better than those with stricture of the aqueduct and in which the procedure is so simple and safe. The earlier the diagnosis is made, the better the operative results will be.

Group II (Under 1 year).—The operative cures obtained in group II are far less than in the preceding one, i. e., in patients over 1 year of age. In the first place, the failures of the operation to sidetrack the fluid into the subarachnoid space are approximately one half, whereas for the patients over 1 year of age failures are very uncommon. The reason for this difference is not

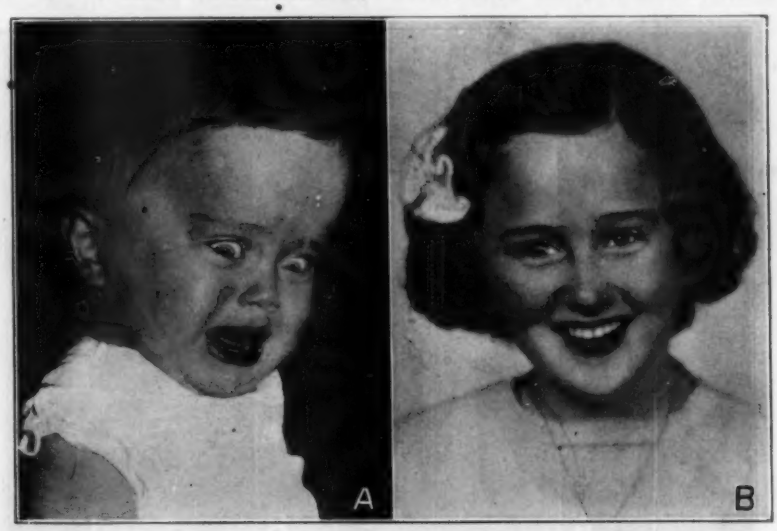

Fig. 12.—*A*, photograph of a patient at the age of 8½ months, showing a marked degree of hydrocephalus. The head then measured 52.5 cm. *B*, the same patient at the present time, twelve years later. The head does not look much oversize, but according to the mother's measurements it is 62.5 cm. in circumference. This may be a mistake, or at least it must include a good deal of hair, because the head does not look so large. The patient is perfectly well.

From the series, 24 are living and cured (figs. 9, 10 and 11). The time since operations is: between six months and one year, 2 cases; between five and ten years, 11 cases; between ten and twenty years, 3 cases, and in 1 case twenty-three and one-half years (fig. 14). Four are mentally retarded in degrees; 1 goes to school but makes little progress; another is in high school but has difficulty keeping up with his classes; the other 2 are morons.

Three patients have greatly defective vision but can see. The vision is not worse than before the operation and in 1 instance has improved a little.

Aside from these defects, which are caused by the long-sustained intracranial pressure, the too clear, and the explanation offered may or may not be correct. It is my impression that the subarachnoid spaces leading from the cisterna interpeduncularis over the cerebral hemispheres may be compressed over such a long period that they may not reopen. In several instances air has been injected intraspinally before operation, and the air has reached but not passed beyond the cisterna interpeduncularis. Since the hydrocephalus in these patients was doubtless present in intrauterine life, these spaces may never have been open and functioning. Consequently, it may be expecting too much to anticipate their reestablishment with uniformity after they have been obliterated for so long. At any rate, these spaces do open in some cases, and when this

obtains the hydrocephalus is cured. For infants, therefore, assurance can never be given that a cure is attainable; it is just a chance, less than even, but the only chance, and it may be worth taking. However, even if he is cured, the chances that the child will be normal are none too good. Even with a moderate-sized head, the cerebral damage is so extensive that one wonders how a normal mentality can ever result, though it occasionally does (figs. 12, 13 and 14). In several of these children, there are such mental deficits and physical infirmities that they had better never been cured. For several years I have made it a rule not to operate on any hydrocephalic infant with a head that is much oversize—perhaps over 50 or 52 cm. At this size one can never be certain of the mental development, which is so varied, and for that reason the infants are probably entitled to any existing doubt; but after this stage there can scarcely be any uncertainty. Obviously the operation should be done at the very earliest time the diagnosis is made. Every week thereafter the cerebral destruction is extensive. Moreover, it is probable—though not certain—that the number of operative cures would be greater in the earlier stages. At present, a baby is rarely referred for operation before a stage has been reached when the mother can make the diagnosis as easily as the physician. With a little more careful observation on the part of physicians, who must bear this responsibility, this picture could easily be changed.

Doubtless the important reasons for the difference in results from operation for hydrocephalus in infants and older children are that (1) in the latter the brain is firmer and more resistant to pressure changes than in infants and (2) the stricture is always partial for some time in children, whereas it is always total in infants. This also means that the cerebral subarachnoid spaces are open and functioning for absorption with the partial occlusions of older patients, and therefore there is every assurance that these spaces will continue to function when the fluid is short-circuited through the third ventriculostomy.

The detailed results in this group of infants—most information is obtained from correspondence—are as follows:

1. Number of patients operated on, 63 (26 females and 37 males).

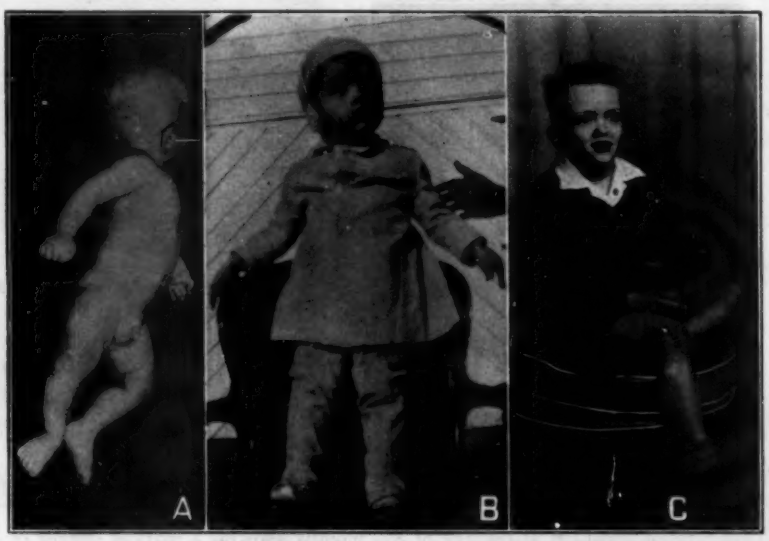

Fig. 13.—*A*, photograph of a patient at the time of third ventriculostomy, April 26, 1939. *B*, the same patient twenty months later. At the time of the first operation the circumference of the head was 52 cm., and the measurement at the time of the last photograph is just the same. *C*, the same patient more than six years after the operation.

2. Number of deaths in hospital, 10; number of survivals, 53.

3. Latest results: Number of patients now living, 21; now dead, 32; no report by letter, 10.

Although there were a few deaths from intercurrent infections and other lesions, most of the patients have probably not been cured.

4. Of the 32 patients who are now dead, 10 died in the hospital; 5 later died in less than a month; 10 died in less than six months; 6, in less than a year, and 1 after twelve and a half years (cause of death not known).

5. Of the 21 who now survive, the time since operation is: for 1, less than six months; for 1,

less than a year; for 5, less than five years; for 8 less than ten years, and for 6 over ten years. The three longest survivals are twelve and one-half, fourteen and one-half, and twenty-three and one-half years (fig. 14).

6. As nearly as can be determined, the hydrocephalus in 12 has been cured. Of these, only 5 have a normal or nearly normal mentality. One of the 12 cured patients is deaf and blind; 2 have clubfeet; 1 is unable to walk; 2 have convulsions, and 7 are decidedly subnormal mentally.

Only once have I seen a hydrocephalic head shrink in size after the operation. In a 3 month old infant, the bones overlapped noticeably at the frontoparietal suture and along the midline. The circumference of the head measured 43 cm. on admission and four months later 39 cm. One could feel very prominent ridges where the bones were overlapping. Four years later the child was walking and talking and appeared to be fairly normal but the head was strikingly microcephalic; unfortunately, photographs were not obtained. The normal growth of the body was in striking contrast to the tiny head. When the child was 4½ years old, a sudden right hemiplegia and aphasia developed and was associated with a high fever—perhaps a vascular accident but certainly not connected with the old hydrocephalus. She survived this but never regained speech or motor power on the right side. Frequent convulsions followed. Six months later she died at the age of 5½ (five and one-fourth years after operation).

Not infrequently one sees slight overriding of the cranial bones soon after operation but, except in this 1 case, no appreciable reduction in the size of the head. The reason doubtless is that the bones are fairly well fixed at the base of the skull and for some distance laterally. Even when the hydrocephalus is cured, the growth of the head may continue at a subnormal rate, therefore stigmatizing the patient with an oversized head of varying degree (see photographs). For the presumably cured patients, the following increases in circumferences of the head have been recorded: (parents' measurements in most cases)

1. Head smaller than before operation after five and one-fourth years.
2. After four, six and ten years, no increase (3 cases).
3. After two years, 1 cm.
4. After five and one-half years, 1 cm.
5. After nine and one-fourth years, 3.5 cm.
6. After five and one-half years, 6 cm.
7. After six years, 5 cm.
8. After twelve years, 10 cm. (measurement questionable; see fig. 12 *B*).

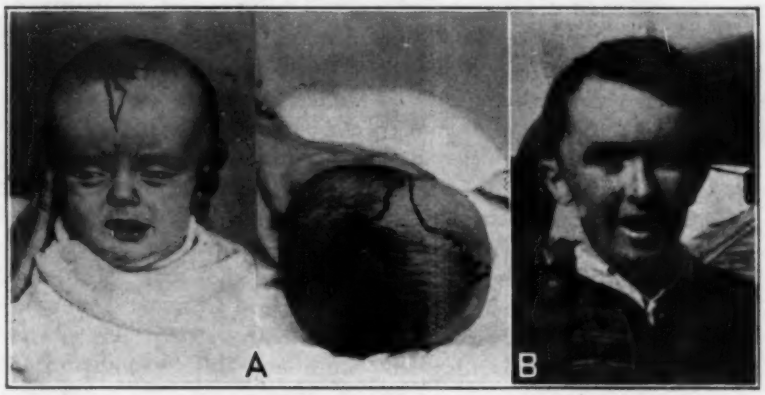

Fig. 14.—*A* and *B*, photographs of the oldest living patient. At the time of operation (April 6, 1921), he was 5 months old and the circumference of the head was 51 cm. The anterior fontanel is outlined in ink. *C*, the same patient twenty years later; he is now 25 years old.

SUMMARY

Strictures of the aqueduct of Sylvius are easily diagnosed in infants by (1) the dye test indicating an obstruction and (2) a low inion.

For children over 1 year old the diagnosis can now usually be made by ventriculography and without operation and frequently without ventriculography. In most of these, a partial occlusion of the aqueduct has doubtless existed for a long period before becoming complete. An oversized head, with (1) Macewen's sign (cracked pot sound) and (2) an inion normally placed or at times lower than normal, indicates hydrocephalus without a space-occuying lesion (a tumor) in the posterior cranial fossa. By exclusion, the lesion is a stricture of the iter.

When ventriculography is used, the shape of the shadow in the aqueduct of Sylvius—funnel shaped or triangular—will frequently make the

diagnosis without an unnecessary cerebellar operation for its disclosure.

A third ventriculostomy—temporal approach—is the operative choice for hydrocephalus due to a stricture of the aqueduct. It is much superior to the anterior approach because (1) external hydrocephalus does not follow; (2) it is not necessary to section a nerve (the optic nerve must be sectioned in the anterior approach), and (3) the scar is under the hair.

Cures are attained in most cases when the patient is more than a year old and in less than half the cases of infants. Excellent results are obtained in the older group. In the younger group—i. e., infants—a perfect result is obtained in very few cases. One may perhaps even question the wisdom of operating on this group, though operation is probably worth while when the head is not over 50 or 52 cm. in circumference at the time of operation.

CHRONIC SCLEROSING PANCREATITIS CAUSING COMPLETE STENOSIS OF THE COMMON BILE DUCT

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All surgeons are familiar with acute pancreatitis of the edematous and necrotic types which are associated with relatively fulminating manifestations but associated with only slight or no obstruction of the common bile duct. They are likewise familiar with temporary complete obstruction of the common duct caused by localized chronic pancreatitis involving the head of the pancreas. These lesions are usually localized to the head of the pancreas and are so hard and nodular that it is difficult to differentiate them from carcinoma. Fortunately, this type of local pancreatitis usually subsides within a few months and thus allows restoration of patency of the common duct. In this presentation we wish to call attention particularly to the other type of chronic pancreatitis, namely, that associated with diffuse atrophy and fibrosis throughout the entire gland. Such a process may produce surprisingly little physiologic or mechanical disturbance. However, on other occasions jaundice may develop and become permanent because of the severity of the sclerosing process involving the common duct. Fortunately, this condition is not common. However, the seriousness of destruction of the terminal end of the common duct by the progressive pancreatitis is sufficiently well appreciated that every effort should be made to treat acute pancreatitis early and eliminate it if possible. We have encountered 3 patients with prolonged obstruction of the common duct produced by chronic fibrosing pancreatitis; the clinical observations and methods of therapy in their cases are discussed later.

Riedel [1] in 1896 was the first to associate chronic, benign, inflammatory lesions of the pancreas with obstructive jaundice. In 1900 and again in a monograph in 1907, Mayo-Robson [2] emphasized the clinical similarity of chronic pancreatitis localized to the head of the pancreas to carcinoma of the pancreas.

A case reported by Carter [3] in 1935 may have been an example of permanent obstruction of the common duct by pancreatitis, but in his case the obstruction had been present only five weeks previous to operation. Yet at autopsy (the patient died of pneumonia) the gland substance was found to be replaced by fibrous tissue in the area surrounding the common bile duct and the common bile duct showed pronounced fibrosis of the wall with narrowing of its lumen, although it retained a normal mucous membrane.

The relative infrequency of stenosis of the common duct secondary to chronic sclerosing pancreatitis is illustrated by the fact that in a review of 80 consecutive cases of stricture of the common duct, Walters [4] did not encounter any in which the stricture was produced primarily by pancreatitis, although in 1 it was secondary to a calcified pancreatic cyst. In 77 of his series, the obstruction had occurred after operation on the gallbladder or bile ducts. Although not all of these were traumatic in origin, enough were to impress one with the extreme seriousness of accidental injury to the common duct.

The etiologic factor in the production of the usual type of acute edematous pancreatitis appears to be strongly related to cholelithiasis; the fact that in most cases the pancreatitis subsides after cholecystectomy is suggestive proof of this relationship, but it is by no means conclusive, since not infrequently cholecystectomy fails to stop the pancreatitis. Occasionally it develops after cholecystectomy. Reference has already been made to the fact that localized pancreatitis in the head of the pancreas, simulating carcinoma, is rather commonly observed by surgeons. For-

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1. Riedel: Ueber entzündliche der Rückbildung fähige Vergrösserungen des Pankreaskopfes, Berl. klin. Wchnschr. **33**:1 and 32, 1896.

2. Robson, A. W. M.: On Pancreatitis with Especial Reference to Chronic Pancreatitis, Its Simulation of Cancer of the Pancreas and Its Treatment by Operation, with Illustrative Cases, Lancet **2**:235-240, 1900; Pancreatitis Due to Direct Extension of a Malignant Growth of the Gallbladder Along the Common Bile Duct and Pancreatic Ducts, ibid. **2**:508-511, 1907.

3. Carter, R. F.: Benign Fibrous Stenosis of the Common Duct, Am. J. Surg. **30**:110-114 (Oct.) 1935.

4. Walters, W.: Strictures and Injuries of Bile Ducts, J. A. M. A. **113**:209-213 (July 15) 1939.

tunately, this process, which frequently produces complete obstruction of the common duct, usually subsides so completely within a few weeks or months that all symptoms disappear. It is our opinion that the surgeon too often attributes the entire success of relief of obstruction to the short-circuiting operation (i. e. cholecystenterostomy). Since we proved beyond doubt that the opening produced by this operation had completely closed on two occasions (four to five months after operation) in 1 of our patients with known complete obstruction of the common duct, we are inclined to believe that in cases of the usual type of cholecystenterostomy the incidence of development of complete stenosis of the suture line in this operation may be high. The seemingly high incidence of success of this procedure for obstruction due to local pancreatitis involving the head of the pancreas may be related to the fact that the pancreatic lesion subsides within a few weeks or months, thereby allowing development of patency of the common duct. The stenosing tendency which we believe occurs in many cholecystenterostomies would therefore not be detected; neither would it be detected when operation is performed for obstruction of the common duct in the usual case of inoperable carcinoma of the head of the pancreas, since the patient is apt to be in the last stages of the metastasizing process by the time the anastomosis is becoming stenosed. Naturally, there is a greater tendency for anastomoses to become stenosed when there is no obstruction distal to the anastomosis. The surgical profession learned this three or more decades ago when they discovered that gastroenterostomies performed for duodenal ulcers without obstruction would not remain open long.

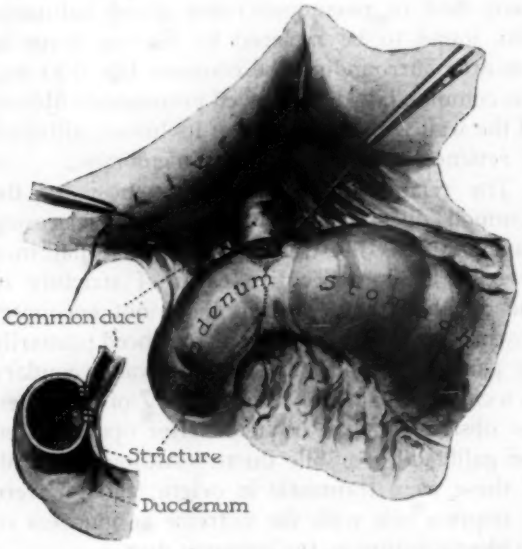

Fig. 1 (Modified from Walters).—Choledochoduodenostomy, anastomosing the mucosa of the terminal end of the remnant of common duct to the mucosa of the duodenum, reenforced with a second row of interrupted cotton or silk sutures, is perhaps the most adaptable procedure for relief of stricture of the terminal end of the common duct. This procedure has a special advantage in cases in which there is a possibility of reopening of the terminal end of the duct; if the terminal end should become patent, the anastomosis would no doubt close and thereby reestablish the original continuity. If the terminal end of the duct is hopelessly damaged, the entire duct may be mobilized and transplanted into the duodenum.

As far as we are aware, there is no information to answer the question as to relationship of local pancreatitis in the head of the pancreas to the development of chronic fibrosing diffuse pancreatitis. We are fairly certain that a great majority of the local lesions in the head of the pancreas subside without consequent involvement of the remainder of the gland, yet it is easily understandable that the lesion in the head might obstruct the major duct (Wirsung) and if collaterals with the minor duct were not profuse an edematous pancreatitis with subsequent fibrosis might develop. It is likewise understandable that a pancreatitis of the diffuse edematous type might lead to a permanent fibrosis, particularly if the lesion were recurrent. For this reason, we feel that recurrent acute edematous pancreatitis is serious, and every effort should be made to eradicate it.

PROTOCOLS AND THEIR ANALYSES

Case 1.—E. M., a white man aged 49, complained of the development of jaundice and anorexia in January 1942. No pain was noted; the urine was bronze in color, and the stools were pale. Three months after onset he was operated on at another hospital, where a tumor mass was found in the head of the pancreas which was causing complete obstruction of the common duct. A cholecystoduodenostomy was done with relief of symptoms. Nine months later, however, his symptoms, including jaundice, returned. Again no pain was noted by the patient, but he had a series of chills followed by fever. Three months after the return of symptoms, he was reoperated on. He was told that the tumor was still present but that there were no metastases. Little or no improvement was noted following this operation. Six months later he was reoperated on for obstruction of the common duct at another hospital, where it was noted that the tumor mass in the head of the pancreas was still present and presumably the cause of the obstruction. A T tube was placed in the common duct, but it was accidentally pulled out a few weeks later. The stools remained acholic except for a period of six months following the first operation; during this interval the cholecystoduodenostomy was apparently patent.

He entered University of Illinois Research and Educational Hospitals one year and nine months after onset of symptoms. He still had acholic stools. A bile fistula in the operative scar was present. The

icterus index was 21. A laparotomy was performed. The head of the pancreas was fibrosed down to a dense scar. The body of the pancreas was much smaller than normal (being about 7 by 2 cm.) and was firm and nodular. It was surrounded by much scar tissue. The liver was moderately enlarged but otherwise appeared normal. The opening in the common duct was located. Opening the gallbladder revealed that the cholecystoduodenostomy was not patent. Saline solution injected into the proximal portion of the common duct came out the gallbladder, proving that the cystic duct was patent. We therefore decided to remodel the cholecystoduodenostomy; this was accordingly done, a large opening being made between the gallbladder and the duodenum. A T tube was placed in the common duct, but it was to be clamped early to encourage function of the cholecystoduodenostomy. For four months following this operation the stools were cholic. After this period they became acholic and remained so until the patient's readmission to the Research and Educational Hospitals eight months after the last operation and two and one-half years after the onset of symptoms. At the time of this last admission it appeared certain that even though the lesion was benign, the chance of reestablishment of the lumen of the pancreatic portion of the common duct by spontaneous means was practically nil. At operation on this admission, it was decided to transplant the common duct into a loop of intestine, since a cholecystoduodenostomy performed on two previous occasions had closed after a few months. Accordingly (on June 5, 1944), as illustrated in figure 2, a choledochojejunostomy was performed, utilizing the Roux principle; the proximal end of the common duct was transplanted into the distal end of the jejunum. To minimize the possibility of intestinal contents regurgitating into the intrahepatic ducts, the wall of the jejunum leading to the anastomosis was enfolded at two or three points to produce a valvular effect. The terminal end of the common duct was closed. It is our opinion that prior to this operation the common duct had been completely stenosed by the chronic pancreatitis for a period of two and one-half years. We feel justified in presuming that the relief of symptoms (i. e., acholic stools) after both cholecystoduodenostomies was due to the function of these anastomoses. The operative procedure finally utilized in this case is, in our opinion, the most nearly ideal, both as to function and as to permanency. In similar choledochojejunostomies for traumatic destruction of the common bile duct, it has frequently seemed desirable to implant a vitallium tube, as initiated by Pearse, but usually only when the stump of the common hepatic duct is so short and small that stricture formation might appear likely. This case has been followed for a period of twelve months after the last operation and the patient has had no recurrence of symptoms. His stools have remained cholic; no jaundice has ensued, and he has had no episodes of chills and fever indicative of cholangitis.

Case 2.—H. S., a white man of 46 years, entered the University of Illinois Research and Educational Hospitals on April 11, 1940, with a complaint of jaundice, associated acholic stools, dark urine, pruritus and abdominal (right upper quadrant) and epigastric pain, all of about six months' duration. The onset of the jaundice was rather sudden, the patient feeling that it occurred over night. His family history was noncontributory but his past history revealed a severe automobile accident in the summer of 1939, at which time his skull was fractured. The physical examination at that time revealed a rather emaciated, jaundiced white man, 41 years of age. The epigastrium was distended, and in that area could be palpated a cystic mass about the size of a large grapefruit. Roentgen ray examinations revealed the mass to displace the pyloric end of the stomach upward and the transverse colon downward, compatible with a pancreatic cyst. Urinalysis gave normal results except for the presence of bile; the blood count revealed a moderate anemia. The blood chemistry was normal except for an icterus index of 40 and a serum amylase activity of 425 units (normal 100 to 175 units). An exploratory operation on April 24, 1940 revealed a pancreatic cyst, which was marsupialized. The tail and body of the pancreas were calcified and crepitated on pressure; the head of the pancreas was normal to palpation. At the time of discharge the icterus index had returned to normal.

A little over two years later, the patient reentered the hospital and complained of jaundice of several

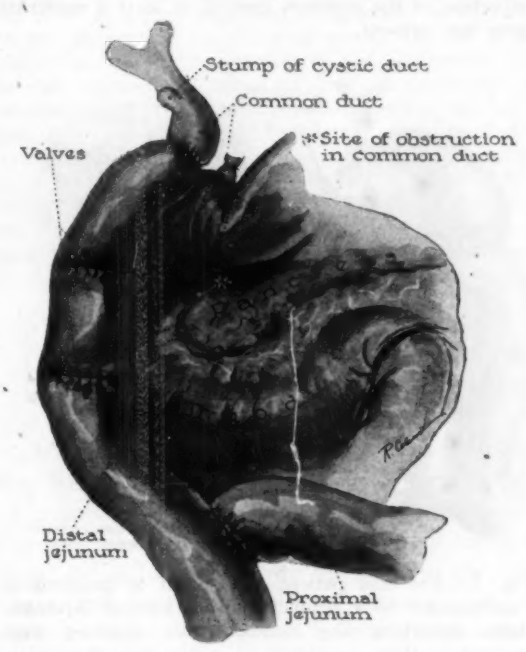

Fig. 2.—In this patient, the terminal end of the duct was obviously hopelessly destroyed by the pancreatitis. A cholecystoduodenostomy, performed or remodeled on two occasions, had closed completely, thereby demanding a different type of procedure. To minimize the chance of cholangitis as much as possible, the terminal end of the duct was anastomosed to a single arm of jejunum, as illustrated. Folds or valves were constructed, in the hope that they would eliminate regurgitation of food and intestinal secretions up into the common duct.

weeks' duration, which was decreasing in intensity. He also complained of a draining abdominal sinus (pancreatic fistula from the marsupialized cyst) since the operation, which would close for periods of two to three days, during which time he would have epigastric discomfort. He stated that since the operation his malaise and fatigue had been so severe that he had been unable to do steady work. Physical examination was essentially noncontributory except for a possible slight icterus and an abdominal sinus draining a small amount of viscid fluid. The laboratory data at that

time were normal except for a low serum amylase activity (75 units). The dextrose tolerance curve was within normal limits. At operation, Aug. 26, 1942, the shrunken, thick-walled cyst was removed and the stump anastomosed to a loop of ileum and an enteroenterostomy performed above this to short circuit food away from the stump of the cyst. The pancreas at this operation was enlarged two to three times normal size and was very hard, but the crepitation which was noted at the previous operation was now absent. The gallbladder was opened and found to contain numerous stones. The gallbladder was not removed, since there appeared to be a strong probability that the persistent pancreatitis might lead to an obstruction of the common duct; we thought that if this happened the gallbladder might be of use for a cholecystoenterostomy. Postoperatively, the pancreatic fistula remained closed, but the cholecystostomy remained patent. It would close intermittently for short periods, causing swelling, and finally open and discharge bile, indicating that an obstruction of the common duct of at least a moderate degree was present.

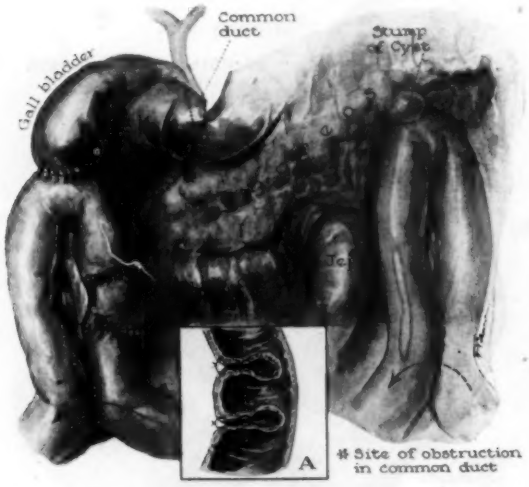

Fig. 3.—For this patient we elected to anastomose the gallbladder to a defunctionalized loop of jejunum, without disturbing the common duct, thinking that there was a slight possibility of restoration of patency of the common duct. We created two folds or flaps in the proximal arm of the jejunum, as was done in figure 2, so that regurgitation would be minimized. The implantation of the stump of the pancreatic cyst into a loop of jejunum was performed at a previous operation and is not related to the correction of the stricture of the common duct.

During a third admission to the hospital in February 1944 (about eighteen months after the cholecystostomy and implantation of the fistula), the patient's stools were bulky, acholic and fatty. Analysis of the duodenal content for enzymes (through the courtesy of Dr. Henry Poncher) revealed an absence of trypsin, indicating complete obstruction of the pancreatic ducts or a destruction of glands of external secretion, probably the former. The icterus index was normal, but there was a history of gray stools most of the time during the preceding several months and drainage of bile from the gallbladder fistula since the cholecystostomy. The fasting blood sugar level had risen to 188 mg. per hundred cubic centimeters, and the dextrose tolerance curve was approaching that of a diabetic person, although there was no sugar in the urine. Roentgen ray visualization of the biliary tract revealed a dilatation of the ducts, with no apparent passage of radio-opaque medium into the intestinal tract after four hours. The patient was readmitted on Sept. 12, 1944. The fistulous tract was still draining bile, and the stools were acholic, although the history revealed that at times they were cholic. The icterus index was normal, but the fasting blood sugar level was 198 mg. per hundred cubic centimeters, indicating that the fibrosing process in the pancreas was increasing and affecting the internal secretions as well as the external. On September 20, he was subjected to a laparotomy. The pancreas was edematous, indurated and much larger than at the previous operation. Moderate fibrosis was developing throughout. The fibrosing and edematous process had enveloped the terminal end of the common duct. However, since at times some bile appeared to get through the sphincter of Oddi and it seemed that subsequent regression of the pancreatic edema might allow the common duct to reopen, it was decided not to transplant the common duct. A cholecystenterostomy, as shown in figure 3, was therefore performed.

On further analysis of the case, the initial attack of jaundice, of six months' duration, was apparently due, at least in part, to pressure of the pancreatic cysts, since it disappeared after marsupialization of the cyst. At the time of the first operation, a diffuse pancreatitis was present, as evidenced by induration of the organ and a pronounced crepitus (due to calcification) on palpation. At the time of the second operation, when the pancreatic cyst was excised (two years and four months after the marsupialization of the cyst), the pancreas was even larger and the crepitus previously noted had disappeared. The jaundice at this time was due to a different cause, for the mechanical effect of a large pancreatic cyst was not present. Intrapancreatic periductal fibrosis was the apparent cause of the stenosis of the common bile duct in that choledocholithiasis had been ruled out at operation. This process seemed to be one of gradual progression involving the entire pancreas, and it is highly probable that our decision to do a simple cholecystenterostomy (instead of an operation of more permanent type, such as the transplantation of the common bile duct into the jejunum) may have been erroneous. It, however, has now been nine months since the cholecystenterostomy, and the patient has had no symptoms referable to biliary obstruction.

Case 3.—G. M., a white man of 37 years, was first admitted to the University of Illinois Research and Educational Hospitals on April 13, 1943. His complaints were typical of chronic cholecystitis with cholelithiasis and choledocholithiasis. According to his history, his complaints dated back to November 1940, when he had his first attack of cramping pain in the right upper abdominal quadrant, associated with nausea, vomiting, jaundice and acholic stools. The pain lasted only about one day, but the jaundice lingered for two weeks. After this attack, he noticed that he frequently had epigastric distress after eating; cabbage or fried foods were particularly distressing. His second, and last, attack came in February 1943 and was similar to but more severe than the first attack. The jaundice lasted a month, and his vague epigastric distress, loss of appetite and malaise persisted until his admittance to the hospital. Examination revealed essentially normal conditions except for a moderate tenderness in the right upper quadrant of the abdomen and a pathologic cholecystogram. At operation, on

April 15, 1943, a chronically diseased gallbladder was removed and a gallstone 1 cm. in diameter was removed from the common bile duct. The pancreas was enlarged one and one-half times and was indurated and nodular. The patient's postoperative period was somewhat stormy because of excessive and prolonged nausea and loss of appetite. He was discharged from the hospital with the T tube in place. Clamping of the tube daily for several hours was well tolerated, and so it was removed on the eighteenth postoperative day. However, removal of the tube was followed in twenty-four hours by cramping epigastric pain, nausea, vomiting and a temperature of 100.6 F. He was again admitted to the hospital (one month following cholecystectomy) with a white blood cell count of 12,000 and an icterus index of 40. These findings, together with pain and tenderness transversely in the epigastrium, made a diagnosis of subacute or acute pancreatitis obvious; it was thought that a mild suppurative cholangitis perhaps accompanied the pancreatitis, but the infection was not severe enough to warrant drainage by operation. The patient responded well to conservative supportive measures and in four days was discharged. He had no complaints then until five months later, when he had a rather sudden onset of epigastric pain radiating to his back, associated with nausea, vomiting, fever and jaundice. After several days in the hospital, with progression of the symptoms, it became evident that the patient was suffering from a rather severe suppurative cholangitis superimposed on the obstruction of the common duct which had again returned. Operation was performed and the common bile duct drained. The pancreas was still indurated and nodular but smaller than at the first operation. At this time it was impossible to pass a probe into the duodenum through the sphincter of Oddi. All manifestations, including jaundice and fever, subsided within a few days following draniage of the common duct. However, during a period of two months' observation, the stools remained acholic. At the end of this time (Dec. 20, 1943), a laparotomy was performed with the idea of anastomosing the common duct to the duodenum. This was accordingly done. A complete stenosis of the terminal portion of the common duct was found; the pancreas was hard, nodular, atrophic and about half the size of a normal pancreas. For reasons to be discussed, a transduodenal choledochoduodenostomy was then done, as illustrated in figure 4. This was one of those occasions (fortunately rather uncommon) when removal of a diseased gallbladder failed to relieve an accompanying pancreatitis.

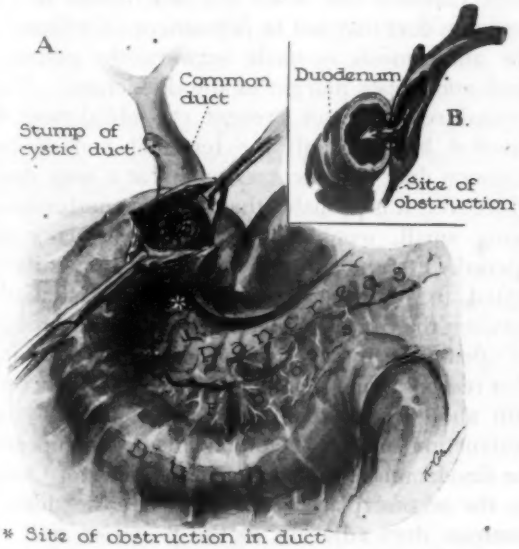

Fig. 4.—A transduodenal anastomosis was performed in this patient because we had already opened the duodenum to inspect the sphincter of Oddi and because we found that the duct was firmly adherent to the duodenum at the point where the anastomosis was made. Actually no sutures would have been necessary, but two or three were taken to maintain fixation in case the adherance of the wall of the duct to the duodenal wall was not solid.

Although this patient had pancreatitis at the first operation, it was thought that the obstruction of the common duct which he had had for two months prior to his initial entrance into the hospital was due to the stone in the common duct. Regardless of the cause of the obstruction, he had a slow recovery for a few weeks because of persistence of the obstruction, but he did recover and remained free of symptoms for several weeks. The obstruction preceding his third, and last, operation was complete but only of two months' duration. Since it was of such short duration, it is perhaps not accurate to consider this as a permanent obstruction, but the fibrosis in the region of the head of the pancreas was so dense and accompanied with so little edema that recovery of patency of the common duct appeared entirely unlikely.

THERAPY

Complete permanent obstruction of the common duct due to chronic pancreatitis is a difficult lesion to treat but much less difficult than obstruction due to complete absence or destruction of the common duct, because the remnant of common duct simplifies the operative procedures. When the obstruction is due to localized pancreatitis involving only the head of the pancreas, the prognosis for spontaneous complete recovery appears to be much better than when a generalized chronic sclerosing pancreatitis is producing a complete obstruction of more than transient type. Therefore, the customary operation of cholecystenterostomy for local pancreatitis in the head of the pancreas appears to be a logical procedure, particularly since, in our opinion at least, the anastomosis will frequently remain open for only a few months, at the end of which time the pancreatitis usually subsides completely with relief of the obstruction. The operation of cholecystenterostomy has one serious disadvantage—namely, development of cholecystitis and hepatitis as has been shown experimentally by Wangensteen [5] and others. Food is bound to collect in the gallbladder unless a type of anastomosis similar to that performed in case 2 (see figure 3) is performed.

5. Wangensteen, O. H.: Cholangitis Following Cholecystenterostomy, Ann. Surg. **87**:54-65 (Jan.) 1928.

Several types of operation are available for the correction of permanent obstruction of the common duct when caused by fibrosing pancreatitis. It would appear obvious that if obstruction is known to be complete, some type of transplantation of the duct, preferably into an isolated loop of intestine, would be indicated. It happens that in the 3 cases described herein three different types of operation were utilized. The indications for each, including its advantages and disadvantages, are briefly discussed.

1. *Cholecystenterostomy.*—One of the most frequently used palliative operations for obstruction of the common duct due to obstructive lesions of the pancreas is anastomosis of the gallbladder to the duodenum or stomach. There has been a trend in recent years to perform the anastomosis between the gallbladder and a loop of jejunum. However, it appears to us that this operation is a relatively poor one except in cases in which the obstruction is thought to be only temporary or the duration of life limited to a period of only a few months. In the first place, our experience suggests that the stoma created by the operation will frequently not remain open permanently, as illustrated by the fact that in 1 of our patients who had had two cholecystenterostomies each closed after a few months, in spite of the fact that the obstruction at the head of the pancreas was complete. As previously stated, another disadvantage of cholecystenterostomy is that infection develops in the gallbladder and ultimately is followed by or accompanied with a severe hepatitis in most cases. Various types of operations have been devised in attempts to prevent this consequent infection. The gallbladder has been threaded through the wall of the stomach or intestine in an oblique fashion; in other procedures, valves have been created and other mechanisms resorted to. It is doubtful to us whether or not these modifications are the means of prevention of infection as long as the food stream is passing directly over the opening of the gallbladder into the intestine.

It appears to us that if the gallbladder is to be used as the conduit for passage of bile from the common hepatic duct to the intestine in patients with permanent obstruction and a life expectancy of several years the gallbladder should be attached to a loop of intestine which is not transporting the food or fecal stream. This can be achieved by one of two methods. One method consists in anastomosis of a loop of jejunum to the gallbladder, with enfolding of the intestinal wall in the proximal loop to block passage of food, and performance of an enteroenterostomy at least several inches from the stoma, as shown in figure 3. In a second method, the jejunum is severed after the Roux principle and the distal arm anastomosed to the gallbladder, as it is to the common duct in figure 2. By utilization of the method illustrated in figure 3, the food stream is completely diverted from the gallbladder. This would obviously eliminate one of the important sources of contamination, although it would not eliminate some regurgitation of intestinal secretions, which according to some observers, Wolfer,[6] Bisgard[7] and others, may be important in the development of inflammation and actual infection in the gallbladder or bile ducts.

2. *Anastomosis of the Common Duct to the Duodenum.*—Such a procedure as performed in case 3 (see figure 4 and also figure 1) should be an ideal one when the gallbladder has previously been removed and when the obstruction in the common duct may not be permanent. Ordinarily, the anastomosis is made between the common duct and upper margin of the duodenum. This procedures does not prevent reestablishment of flow of bile through the terminal end of the common duct if it becomes patent at a later date. Moreover, it is probable that such an anastomosis, being small, would close after the duct itself opened. For the patient whose operation is illustrated in figure 4, we made the anastomosis between the common duct and duodenum through an opening in the duodenum. This was done for two reasons: In the first place, we were not certain about the extent and completeness of the obstruction in the common duct and opened the duodenum to visualize the sphincter of Oddi. In the second place, we found that the dilated common duct adjacent to the posterior wall of the duodenum was actually adherent to the duodenum. This allowed us to make an anastomosis by cutting through the duodenum into the common duct, with utilization of very few sutures and with practically no danger of leakage. In average circumstances, however, making the anastomosis between the superior edge of the duodenum and the common duct (see figure 1) would be a more desirable procedure than doing the anastomosis inside the duodenum, as illustrated in figure 4.

3. *Transplantation of the Duct into the Intestine.*—When the obstruction is of a permanent

6. Wolfer, J. A.: Further Evidence That Pancreatic Juice Reflex May Be Etiologic Factor in Gallbladder Disease, Ann. Surg. **109**:187-192 (Feb.) 1939.

7. Bisgard, J. D., and Baker, C. P.: Studies Relating to the Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis, Ann. Surg. **112**:1006-1034 (Dec.) 1940.

type, the most obvious method of correction would be transplantation of the duct into a loop of intestine. The duct can be threaded obliquely through the wall of the intestine in an effort to prevent regurgitation of infective material into the duct. We are not convinced, however, that this procedure is as safe from the standpoint of prevention of infection as transplantation of the duct into a blind loop of intestine, similar to the gallbladder anastomosis, illustrated in figure 3, or transplantation of the duct into the distal end of the cut jejunum, after the Roux principle, as shown in figure 2. When the principle shown in figure 2 is utilized, the only danger of inflammation would be that associated with the chemical effect of the secretions of the intestine, largely because the isolation of the loop and the valves made in the wall would prevent reflux of food into the duct. These valves [7a] may be made in one of two ways: The simplest method is to enfold the wall of the intestine with several interrupted sutures. The more complicated method is to make a horseshoe-shaped incision through the wall of the intestine, with the base placed proximally. The flap is pushed into the lumen and the opening closed. This produces a perfect type of valve, at least temporarily, although we are not yet certain as to whether the valve is maintained as a distinct flap or is malformed through atrophy. These valves are discussed in more detail by Cole, Ireneus and Reynolds.[8] Experiments are being conducted to determine the exact fate of these valves.

SUMMARY

A thorough understanding of the general and local operative findings, as well as the prognosis of chronic pancreatitis, is of utmost importance to the abdominal surgeon, both from a diagnostic and from a therapeutic standpoint. Chronic pancreatitis localized to the head of the pancreas, producing temporary complete obstructions of the common bile duct, is extremely difficult to differentiate from carcinoma of the head of the pancreas without a deep biopsy from the lesion. This type of pancreatitis is adequately treated by means of a palliative cholecystenterostomy, for the pancreatic obstruction to the biliary passage is usually relieved before the cholecystenterostomy has stenosed.

In the even more rare type of diffuse chronic sclerosing type of pancreatitis, one is dealing not only with a possibility of atrophy of the glands of both internal and external secretions of the pancreas but with the gradual, permanent and eventually complete stenosis of the pancreatic portion of the common bile duct. The first 2 of the 3 patients presented have mild diabetes, indicating that the pancreatic destruction must have been very extensive.

Operative therapy must be directed at establishing a permanent, nonstenosing communication between the suprapancreatic portion of the common bile duct and the intestinal tract. In addition, the regurgitation of food and intestinal secretions must be prevented as much as possible.

Of several operative procedures that have been described, each has some individual merit. In our opinion, the procedure of choice would be an anastomosis of the proximal stump of common duct to the duodenum (see figure 1) or the anastomosis of the proximal end of the common bile duct to the blind end of a single arm of jejunum, utilizing the Roux principle, as shown in figure 2. Into this blind loop of jejunum, through which food does not ordinarily pass, valves, as previously described, are placed to act as baffles to help prevent regurgitation of food. The procedure illustrated in figure 1 is much shorter than that in figure 2 and probably only slightly more likely to give rise to cholangitis than that shown in figure 2; it therefore would appear to be an appropriate method. A side to side anastomosis, as illustrated in figure 1, has the added advantage of allowing function of the terminal duct to be resumed if the pancreatic lesion should clear sufficiently to allow relief of the obstruction. If the terminal end of the duct is hopelessly destroyed, the duct may be mobilized and either a transplantation into the duodenum or an anastomosis performed, as in figure 2. If the latter procedure is used, a vitallium tube may or may not be used, depending on the size of the common duct.

To date, the postoperative course in each of the 3 cases [9] presented has been entirely satisfactory. None of the 3 patients has had recurrence of jaundice or chills, which would be expected if a stricture reformed or cholangitis developed.

7a. No claim is made for originality in the design of these valves, since innumerable types have been described in the medical literature.

8. Cole, W. H.; Ireneus, C., and Reynolds, J. T.: The Repair of Stricture and Absence of the Common Duct, with Particular Reference to the Vitallium Tube, Ann. Surg., to be published.

9. Since this manuscript was submitted for publication 1 of these patients (case 1) has begun to have very troublesome transverse pain in the epigastrium without jaundice or chills. In the absence of obstruction of the duct we have assumed the pain to be related to continuation of the pancreatitis process.

PENICILLIN

ITS TOPICAL USE AS A BACTERIOSTATIC AGENT FOR THE PALLIATIVE TREATMENT OF CHRONIC STASIS ULCERS OF THE LOWER EXTREMITIES

DURWARD L. LOVELL, M.D.
DURHAM, N. C.

Chronic stasis ulcers of the lower extremities are a frequent complication of varicose veins and thrombophlebitis. In the presence of chronic venous stasis the skin shows nutritional disturbances, such as atrophy, pigmentation and induration. An ulcer usually develops at the site of previous pigmentation and induration or occurs suddenly after thrombosis of a cutaneous vein, over which the skin ulcerates. Slight trauma may be the immediate cause of such an ulcer. In the early acute stages these ulcers fail to heal, because of anoxemia due to stasis and secondary infection. When they become chronic, an additional factor, i. e., poor local arterial blood supply, prevents spontaneous healing. All types of treatment are directed toward relieving the venous hydrostatic pressure and reducing the local infection. The palliative methods used for the ambulatory patient accomplish this by elastic support of the extremity and topical application of a bacteriostatic agent. The organism commonly responsible for the infection in these cases is Staphylococcus aureus. Keefer and associates [1] have reported that penicillin exerts a pronounced bacteriostatic effect against many gram-positive organisms when administered topically. The purpose of this paper is to report the results of treatment in 10 cases of chronic stasis ulcers, using penicillin as a bacteriostatic agent.

Palliative treatment is frequently advised as a preliminary procedure before ligation, excision or injection of varicose veins. It is also advised for use in cases in which age, infirmity or prejudice against any other procedure prevents more radical measures. Palliative therapy is unsatisfactory in those cases in which there are extensive fibrosis and poor arterial blood supply. Epithelization is delayed because of insufficient granulation tissue in the base of the ulcer. It is thought that radical excision of the lesion and the surrounding fibrosis is the treatment of choice, unless operation is contraindicated.

From the Department of Surgery, Duke University School of Medicine and Duke Hospital.

1. Keefer, C. S., and others: Penicillin in the Treatment of Infections: Report of Five Hundred Cases; Statement by the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council, J. A. M. A. **122**:1217-1224 (Aug. 28) 1943.

REPORT OF CASES

It was desirable to observe the effect of penicillin on the local infection and the rapidity of epithelization. For this reason, the patients selected for treatment varied considerably with regard to the duration and the amount of infection present. Some of the ulcers were acute and painful, having soft edges, abundant granulations and extensive infection. Others had been present for many months, with extensive fibrosis around the edges and scanty granulations due to poor arterial blood supply. In practically all cases the predominating organism grown from the lesions was Staph. aureus. The ulcers were cleaned, and a gauze dressing saturated with isotonic solution of sodium chloride containing 500 units of the sodium salt of penicillin per cubic centimeter was applied directly to the ulcer. An Unna paste boot was then applied, extending from the base of the toes to a point just below the knee. All patients residing within a short distance from the hospital returned for dressings twice each week, and those who had transportation difficulties returned at weekly intervals.

CASE 1.—A. K., a 24 year old white man, had a recurrent chronic ulcer on his right leg for six years. When he was first seen at Duke Hospital, examination revealed a large ulcer above the medial surface of the right ankle. Considerable secondary infection and cellulitis were present. The base of the lesion was covered with abundant granulation tissue, and there was minimal fibrosis of the edges (fig. 1*A*). Hemolytic and nonhemolytic Staph. aureus organisms were grown from the surface. Pathologic sections of a biopsy specimen taken from the edge of the ulceration revealed nonspecific chronic inflammation. The Wassermann reaction was negative. Examination of the right thigh and leg revealed numerous varicose veins. A diagnosis of varicose veins of the right lower extremity with chronic stasis ulcer was made. On Aug. 2, 1944, a penicillin dressing and an Unna paste boot were applied. Dressings were changed twice each week. After the first application of penicillin, considerable improvement was noted, and the surface of the ulcer began to epithelize. The film of exudate on the surface of the granu-

lation tissue disappeared, and the base of the lesion appeared clean and granular. On September 30, eight weeks after penicillin therapy was instituted, the lesion was completely healed (fig. 1 *B*).

In this case an acute ulcer with extensive secondary infection responded well to local penicillin therapy. The arterial blood supply to the lesion was good and epithelization occurred rapidly after the infection and stasis were corrected.

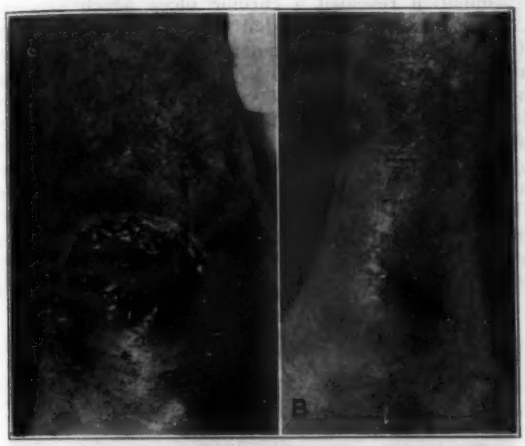

Fig. 1 (case 1).—*A*, appearance of the ulcer at the beginning of penicillin therapy; *B*, appearance after treatment for eight weeks.

Case 2.—B. M., a 33 year old white woman, had recurrent ulcers of thirteen years' duration on both legs. The first ulcer appeared after pregnancy and persisted for four years. She was examined at Duke Hospital in June 1940, and at that time there was a chronic ulcer which had been present for ten months on her left leg. She was treated with Unna's paste boots and local applications of gentian violet medicinal. The ulcer healed after seven months' treatment. She was admitted to the hospital in February 1941, at which time bilateral high ligation of the saphenous veins and excision of varicose veins were performed. She returned eight months later, the ulcer having recurred. The same treatment was given, and the ulcer healed in eighteen weeks. She returned in June 1943 with an ulcer on the right leg and three ulcers on the left leg, which had been present for two months. The granulation tissue in the base of the lesions was covered with a layer of fibrinopurulent exudate (fig. 2 *A* and *C*). Hemolytic Staph. aureus and Bacillus proteus organisms were grown from the surface. There were numerous varicose veins on both legs. A diagnosis of chronic stasis ulcers of the lower extremities was made. Penicillin dressings and Unna's paste boots were applied and changed twice each week. Improvement was rapid, and clean granulation tissue appeared on the base of the ulcers. Within ten days, the small ulcers on the left leg were healed. After seventeen days of treatment, the lesion on the right leg was healed. The larger ulcer on the left leg healed after forty-one days of treatment (fig. 2 *B* and *D*).

The lesions in this case had been present for two months. There was extensive infection, but rapid improvement was obtained with penicillin dressings. There was minimal fibrosis around the edges, and as soon as stasis and infection were corrected epithelization occurred rapidly. The previous ulcers had been treated with gentian violet medicinal, and they healed after periods of seven months and eighteen weeks, respectively. Better results were obtained with penicillin.

Fig. 2 (case 2).—*A*, lesions on left leg at the beginning of penicillin therapy; *B*, lesions on left leg healed after treatment for six weeks; *C*, lesion on right leg at the beginning of penicillin therapy; *D*, lesion on right leg healed after treatment for seventeen days.

Case 3.—E. McL., a 36 year old Negro woman, had recurrent ulcers on her left leg for three years. She was examined at Duke Hospital in June 1943, and at that time there were two infected ulcers on the medial

surface of the left leg. These lesions had been present for four weeks. A diagnosis of stasis ulcers was made. She was treated with local application of 5 per cent sulfathiazole ointment and Unna's paste boots. The dressings were changed once each week for a period of two months, without any definite improvement. Epithelization did not occur, and the granulation tissue in the base of the ulcer was covered with a thick layer of fibrinopurulent exudate (fig. 3 *A*). Staph. aureus or-

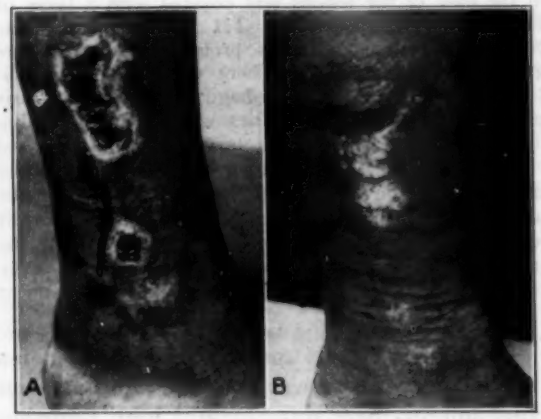

Fig. 3 (case 3).—*A*, lesion at the beginning of penicillin therapy; *B*, healed lesion after treatment for ten weeks.

ganisms were grown from the surface of the lesions. In July 1943, penicillin was substituted for the sulfathiazole ointment, and dressings were changed twice each week. There was rapid improvement. After one week of treatment with penicillin, the granulation tissue was clean and granular. The film of purulent exudate

Fig. 4 (case 4).—*A*, lesion at the beginning of penicillin therapy; *B*, healed lesion after treatment for five weeks.

disappeared, and epithelium began to grow over the surface. On October 15, ten weeks after penicillin therapy was started, the ulcer was completely healed (fig. 3 *B*).

The lesions in this case failed to improve satisfactorily with 5 per cent sulfathiazole ointment and Unna's paste boots, but they responded readily after penicillin was substituted for the sulfathiazole.

Case 4.—R. B., a 47 year old white woman, had varicose veins and recurrent ulcers on her left leg for eighteen years. During her last pregnancy she had eclampsia and phlebitis. Varicose veins subsequently developed. Chronic ulcers had appeared and healed spontaneously during the period of eighteen years. She was seen at Duke Hospital on July 24, 1944, and examination revealed a chronic ulcer which measured 2 by 2.5 cm. on the medial surface of the left ankle (fig. 4 *A*). The lesion had appeared three weeks previously. Granulation tissue on the ulcer was scanty, and there was moderate fibrosis of the edges. Extensive infection was present. Staph. aureus, Staphylococcus albus and B. proteus organisms were grown from the surface. The Wassermann test elicited a negative reaction. There were numerous varicose veins on the thigh and leg. A diagnosis of chronic stasis ulcer was made. Penicillin dressings and an Unna paste boot were applied and changed twice each week. The infected parts improved rapidly. The lesion was completely

Fig. 5 (case 5).—*A*, lesion at the beginning of penicillin therapy; *B*, healed lesion after treatment for seventeen weeks.

healed August 28, five weeks after treatment was instituted (fig. 4 *B*).

Although in this case the ulcer was surrounded by a moderate amount of fibrosis and the granulation tissue was scanty, it responded well to penicillin therapy. Ulcers in this region are resistant to treatment and heal slowly after extensive fibrosis has occurred. Although this ulcer healed rapidly, it was extremely painful until epithelization was complete.

Case 5.—M. E., a 43 year old Negro woman, had had numerous varicose veins on the left leg for four years and chronic recurrent ulcers on the same leg for one year. Operation had been advised but refused. She was seen at Duke Hospital on Aug. 31, 1944, and examination revealed an infected ulcer measuring 3.5 by 3.5 cm. on the lateral surface of the left leg. The base of the ulcer was filled with granulation tissue and covered with a film of fibrinopurulent exudate. There was considerable fibrosis around the edges. Staph. aureus organisms were grown from the lesion. Five

per cent sulfathiazole ointment and an Unna paste boot were applied and changed weekly for two weeks without any definite improvement. The infection persisted, and there was no evidence of epithelization (fig. 5 *A*). On September 14 penicillin was substituted for the sulfathiazole. There was rapid improvement, but the epithelization was slow because of extensive fibrosis and poor arterial blood supply. The lesion was completely healed on Jan. 26, 1945, seventeen weeks after penicillin therapy was instituted (fig. 5 *B*).

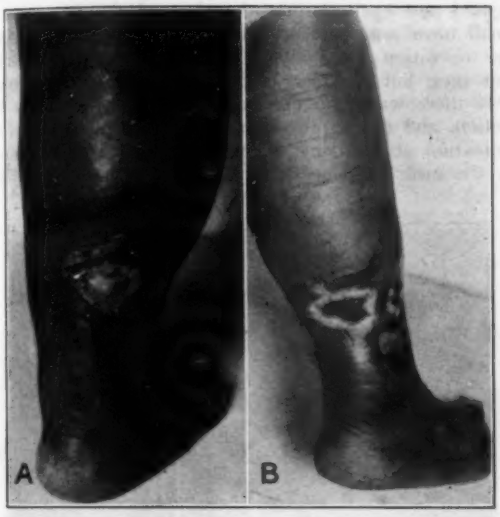

Fig. 6 (case 6).—*A*, lesion at beginning of penicillin therapy; *B*, condition of the ulcer after treatment for seventeen weeks.

This case illustrates the difficult problem of treating chronic ulcers of this type by palliative methods. The infection in this case responded more readily to penicillin than to sulfathiazole. Healing was delayed, however, after the infection subsided. This was thought to be due to poor arterial blood supply caused by extensive fibrosis.

Case 6.—M. B., a 33 year old Negro woman, had a large ulcer on her right leg for three years. The ulcer began after a trivial injury and failed to heal after the local application of numerous types of ointment. She was first seen at Duke Hospital on May 25, 1943, at which time examination revealed extensive varicose veins on her right leg. There were two large ulcers on the lateral surface of the leg which were extensively infected, having a greenish necrotic base and extending deep into the subcutaneous tissue. The reaction to the Wassermann test was negative. Five per cent sulfathiazole ointment and Unna's paste boots were applied weekly for a period of seven weeks, without any definite improvement of the infected parts (fig. 6 *A*). On July 20 penicillin was substituted for the sulfathiazole ointment. Improvement was rapid, and granulation tissue appeared on the base of the ulcer. This patient returned for treatment for a period of seventeen weeks, and at the end of this time the ulcer had become greatly reduced in size. The small ulcer was almost completely healed at this time (fig. 6 *B*). The patient discontinued treatment after seventeen weeks, and further follow-up could not be obtained.

In this case a chronic ulcer with very extensive infection failed to respond to treatment with sulfathiazole ointment. The infection cleared rapidly with penicillin. Epithelization began as soon as the infection subsided.

Case 7.—E. M., a 36 year old Negro woman, had varicose veins and recurrent ulcers on her left leg for four years. She was first seen at Duke Hospital on Dec. 8, 1944, and examination revealed an ulceration on the medial surface of the left leg with considerable secondary infection. The surrounding skin was indurated and deeply pigmented. There were numerous varicose veins on the lower part of the leg. There was mild fibrosis of the edges of the lesion. Staph. aureus organisms were grown from the surface of the ulcer. The Wassermann test elicited a negative reaction. A diagnosis of chronic stasis ulcer was made. Five per cent sulfathiazole ointment and Unna's paste boots were applied, the dressings being changed weekly for a period of two months. During this time considerable infection persisted, and the epithelization occurred very slowly. On Feb. 1, 1945, a large ulcer with a fibrinopurulent exudate on the surface was still present (fig. 7 *A*). At this time penicillin dressing with an Unna paste boot was applied. Dressings were changed twice each week. With this treatment the exudate on the surface disappeared, and the ulcer began to heal rapidly. On April 17 the ulcer was completely epithelized, ten weeks after penicillin therapy was instituted (fig. 7 *B*).

In this case a lesion responded to topical applications of penicillin more readily than to sulfathiazole ointment.

Fig. 7 (case 7).—*A*, lesion at the beginning of penicillin therapy; *B*, healed lesion after treatment for ten weeks.

Case 8.—M. D., a 42 year old Negro woman, had thrombophlebitis five years ago. Varicose veins subsequently developed. An ulcer appeared on her left leg, which healed and recurred numerous times during the five year period. She was seen at Duke Hospital Aug. 1, 1944, and examination revealed an ulcer above the medial surface of the left ankle. There were marked fibrosis around the edges of the lesion and considerable infection. There were numerous varicose veins on the thigh and leg. Nonhemolytic Staph. aureus organisms were grown from the surface. Local applications of gentian violet medicinal and Unna paste boots were

applied weekly for a period of two months, without improvement. There was an exacerbation of the secondary infection, and the ulcer appeared to increase in size. Granulation tissue was scanty, and the arterial blood supply was poor (fig. 8 *A*). On Oct. 4, 1944, penicillin dressing and an Unna paste boot were applied and changed once each week. There was rapid improvement of the infection. Epithelization occurred

Fig. 8 (case 8).—*A*, lesion at the beginning of penicillin therapy; *B*, healed lesion after treatment for twenty-four weeks.

slowly, however, and the ulcer was not completely healed until March 21, 1945, twenty-four weeks after penicillin therapy was instituted (fig. 8 *B*).

This case is one in which there was extensive fibrosis in the edges of the lesion and epithelization occurred slowly because of the poor blood supply. In such cases ordinarily treatment consists in complete excision of the ulcer and the surrounding fibrosis and covering of the defect

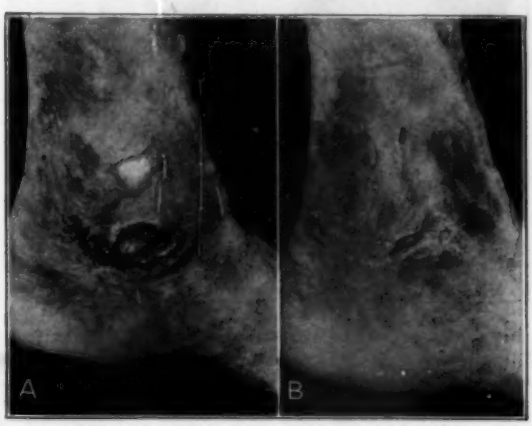

Fig. 9 (case 9).—*A*, lesion at the beginning of penicillin therapy; *B*, ulcer after treatment for seven months.

with a skin graft. Palliative therapy was continued in this case in an effort to determine the effect of local infection on the rate of epithelization. Soon after use of penicillin dressings was started, the base of the lesion became clean and granular, but this apparently had little effect on the rate of epithelization. It is thought that slow healing was due to pure arterial blood supply.

Case 9.—A. B., a 26 year old white man, had varicose veins and recurrent ulcers on his left leg for five years. The ulcer first appeared in February 1940, after trauma received from a plaster cast, which had been applied for a fractured femur. The ulceration healed but recurred. Numerous varicose veins subsequently developed. He was admitted to Duke Hospital in December 1943, at which time varicose veins of the lower extremities were ligated and excised. At the time of the operation a small ulcer was present just beneath the ankle. After the operation the patient continued to wear elastic bandages, but the ulcer failed to heal. In September 1944 there was an acute exacerbation of secondary infection, and the lesion became extremely painful. Examination at this time revealed a small infected ulcer on the medial surface of the left leg below the ankle.

Fig. 10 (case 10).—*A*, lesions at the beginning of penicillin therapy; *B*, lesions after treatment for eight months.

There were numerous varicose veins beneath the skin of this region, and there was extensive fibrosis of the edges of the ulcer (fig. 9 *A*). Staph. aureus organisms were grown from the surface of the lesion. On September 14 penicillin dressing and an Unna paste boot were applied. The patient returned for weekly treatments.

The infection cleared rapidly, but granulation tissue grew very slowly in the base of the ulcer. After seven months' treatment, the ulcer was reduced in size but had not completely healed (fig. 9 *B*).

This is a case in which surrounding fibrosis, creating poor arterial blood supply, prevented healing. Although the infection and stasis had been corrected, epithelization was delayed.

Case 10.—E. S., a 62 year old white man, received a trivial injury to the lower anterior surface of his left leg one year prior to examination. An ulcer

developed in this region and failed to heal. Within two months after injury, two other ulcers developed. A fungus infection was suspected, and the patient was given numerous roentgen ray treatments over the lower leg. This resulted in pronounced induration and fibrosis of the skin over the entire leg. Numerous ointments were used locally, and elastic stockings were worn to prevent stasis, but the ulcers failed to heal. He was first seen at Duke Hospital on July 26, 1944, and examination revealed four ulcerations varying from 0.5 to 5 cm. in diameter over the anterior surface of the left leg. They were surrounded by extensive fibrosis, and the granulation tissue was covered with fibrinopurulent exudate (fig. 10 *A*). Hemolytic Staph. aureus organisms were grown from the surface of the ulcers. A Wassermann test elicited a negative reaction. Pathologic section of a biopsy specimen taken from the edge of the largest ulcer revealed chronic nonspecific inflammation. No fungus organisms were seen. A diagnosis of chronic stasis ulcers was made. The patient refused operation. Penicillin dressing and an Unna paste boot were applied and changed weekly. There was rapid improvement. The small ulcer at the lower end of the leg healed in one week, the lesion on the upper part of the leg healing in three weeks. The two ulcers in the center healed much more slowly. The small lesion healed in four months, and the larger one had not completely healed after eight months' treatment. Another small ulcer subsequently appeared after eczematoid dermatitis. Figure 10 *B* shows the condition of the large ulcer after a period of eight months' treatment. Little infection was present, but the granulation tissue was scanty because of poor arterial blood supply.

This case is similar to the one previously presented. The infection cleared rapidly after penicillin was applied, and it is thought that slow healing was due to poor arterial blood supply. Palliative treatment in such cases is not satisfactory.

COMMENT

The management of chronic stasis ulcers of the lower extremities is difficult. Palliative treatment is justified in some cases, and the methods used for the ambulatory patient consist of elastic support of the extremity to relieve the venous hydrostatic pressure and topical application of a bacteriostatic agent to combat infection. In 10 cases penicillin was used topically as a bacteriostatic agent. Elastic support was supplied to the extremity by application of Unna's paste boots. The local infection in all cases subsided rapidly after the application of penicillin. Penicillin appeared to be far superior to other bacteriostatic agents in cases in which there had been previous treatment. The infection was controlled more readily when the dressings were changed twice each week. This was probably due to the fact that penicillin loses its strength after being at body temperature for several hours. Rapid healing occurred in 5 cases of early ulceration in which there was minimal fibrosis around the edges and good arterial blood supply. The time required for healing in these cases varied from ten days to ten weeks. In 1 case the patient failed to return for treatment until the lesion was healed, but when she was last seen the infection was under control and epithelization was occurring rapidly. Healing in the other 4 cases was slow, although the infection was under control. This was thought to be due to poor arterial blood supply. It is my opinion that in such cases treatment should be radical excision of the ulcer and covering of the defect with a skin graft, unless operation is contraindicated.

CONCLUSIONS

The secondary infection in chronic stasis ulcers responds readily to topical applications of penicillin. It is thought to be superior to other bacteriostatic agents that are generally used for this purpose. In the early stages rapid healing occurs when the infection and stasis are controlled. Healing is delayed in the cases of chronic ulceration because of extensive fibrosis of the edges and poor arterial blood supply.

TRANSTHORACIC OPERATIVE APPROACH FOR TRAUMATIC LESIONS OF THE SPLEEN

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Splenic injuries are not uncommon among battle casualties and are usually associated with other intra-abdominal or intrathoracic injuries. Today the consensus is entirely in favor of splenectomy for splenic injury, and splenic suture has been abandoned, so far as we have been able to determine. The preferable incision for splenectomy in these circumstances depends to some extent on concomitant injuries.

While statistics for this theater of operations are not available at present, observation of patients admitted from forward hospitals and conversation with other surgeons give the impression that the majority of splenectomies are performed through a vertical left rectus incision with or without a transverse extension. A few cases have been observed in which a transverse incision has been used. We and others have utilized a third operative approach, namely, the transthoracic route. In a survey of the literature which our facilities make available, we have been unable to find references to the use of this approach for traumatic lesions of the spleen. Lahey and Marshall have mentioned splenectomy incidental to transthoracic total gastrectomy and commented on the ease of the procedure. Such information as is available at this time is insufficient to determine priority in the use of the transthoracic approach for traumatic splenic lesions.

Our interest in the procedure was awakened by the arrival of 2 convalescent patients on whom transthoracic splenectomies had been performed in forward hospitals, where, of necessity, most splenectomies are performed. We were impressed by their smooth convalescence and the absence of postoperative complications, as well as by the obvious integrity of the abdominal wall. During our service at a base hospital and during tours of duty at evacuation hospitals, we have performed several more splenectomies by the transthoracic route and have treated postoperatively 20 patients operated on elsewhere. This added experience has convinced us that this is the preferable route for splenectomy, whether or not it is associated with intrathoracic injury. Obviously there will always be cases in which concomitant intra-abdominal injuries may dictate the use of another route, but, whenever possible, we shall employ the transthoracic approach. In this connection, it has been our impression that the usual long rectus incision predisposes to weakness of the abdominal wall, owing to the necessary section of two or more intercostal nerves. It is the purpose of this article to demonstrate the ease and facility of the transthoracic approach.

At first sight it may seem that, although splenectomy may be feasible through the transthoracic approach, exploration of the peritoneal cavity will be, at best, limited. In our experience this is not true, and it has been possible to explore the entire small intestine, the transverse and descending portions of the colon and the stomach and proximal portion of the duodenum, although in 1 case a perforation high on the lesser curvature of the stomach could not be visualized.

In our cases the operation has been performed with the patient under anesthesia induced with ether and oxygen endotracheally administered, and we feel that this is the most suitable method, permitting, as it does, reexpansion of the lung before closure of the wound.

The chest is opened by an anterolateral incision, either through the eighth interspace or through the bed of the eighth or the ninth rib. Resection of the rib seems to give a little better exposure; though, with the Flick rib spreader, adequate exposure is obtained by either method. We have not found it necessary to crush the phrenic nerve in order to produce a flaccid diaphragm. The diaphragm is incised radially, and the spleen is located and brought into the operative field without difficulty. Adhesions may be removed by sharp dissection under complete visual control. The pedicle may be ligated en masse or by separate dissection of the vessels, according to the desire of the operator. Any

desired further exploration is then performed. The ease with which all manipulations about the spleen may be carried out is a pleasant surprise, and the actual splenectomy is much easier than through any abdominal incision. The diaphragm is closed with two rows of interrupted silk or fine chromic sutures. Whether or not the pleural cavity should be drained routinely is unsettled. One of us favors nondrainage and tne other, a temporary waterseal drainage through an intercostal catheter.

It cannot be denied that in theory, at least, there are dangers in connection with this approach not associated with an abdominal incision. The possibility of empyema must be kept in mind, as well as the possibility of late herniation through the sutured diaphragm. These complications have not occurred in our cases, nor have we heard of their occurrence in the cases of other surgeons in this theater.

REPORT OF CASES

CASE 1.—A soldier, aged 24, was wounded at 4 p. m., Feb. 18, 1944, suffering two shell fragment wounds in the left posterior part of the chest and a penetrating wound in the left leg. The patient's treatment at the forward hospital consisted of closure of the sucking wounds by a petrolatum gauze pack, sulfanilamide therapy and administration of plasma and morphine sulfate. He was in fair condition on arrival at this hospital, on the evening of February 20. There were two large thoracic wounds packed with petrolatum gauze, one about 4 inches (10 cm.) long over the left scapula and the other in the posterior axillary line in the eighth interspace. Roentgenologic examination the following morning showed fractures of the eighth and ninth ribs of the left side, fluid in the left pleural cavity and a large metallic foreign body in the lower part of the abdomen. There was little respiratory embarrassment. At this time, there were spasm and increased tenderness in the left upper quadrant of the abdomen, and a diagnosis of lacerated spleen was postulated. The patient was given a transfusion of 1,000 cc. of whole blood, and an operation was performed.

Operation was performed Feb. 21, 1944, and the following postoperative diagnoses were made: two penetrating wounds in the left posterior wall of the chest, laceration of the lower lobe of the left lung, laceration of the left side of the diaphragm, contusion, laceration of the spleen and presence of an intraperitoneal foreign body.

Operation.—An anterolateral thoracotomy incision was made through the bed of the fractured ninth rib on the left side after excision of the wound. About 6 inches (15 cm.) of rib was removed subperiosteally, anterior to the fracture site. There was a 3 inch (8 cm.) defect in the continuity of the rib owing to the fracture. The pleura was opened. About 400 to 500 cc. of blood was evacuated. A fragment of rib about 3 inches long protruded from a laceration in the lower lobe of the left lung. There was an area of hematoma about the laceration. There was no free bleeding at this time. The large fragment and two small fragments were removed from the lung, and the laceration was closed with two mattress sutures of 00 chromic surgical gut. There was a laceration of the left lateral leaf of the diaphragm, through which omentum protruded. The opening was enlarged radially for about 5 inches (13 cm.). The stomach was intact, and there were free blood and clot in the peritoneal cavity, but no evidence of peritoneal irritation was observed. The spleen was badly contused and showed a superficial lacerated wound. Splenectomy was easily performed. The transverse and hepatic flexures of the colon were intact. A large metallic foreign body, about 2 cm. in diameter, was found lying in the pelvis, completely encapsulated by omentum. It was removed with the surrounding omentum. A small amount of pus was observed about the metallic foreign body. The diaphragm was repaired by two layers of Lembert sutures of 00 chromic surgical gut. The wound of the chest was closed in layers, after the lung had been reexpanded. The posterior wound of the chest was débrided, and no intrapleural communication was noted. The wound of the thigh was then débrided, and both wounds were dressed with petrolatum gauze and sulfanilamide crystals.

Pathologic Report.—Observations: In several sections, the capsule of the spleen was covered by a layer of blood. The capsule and trabeculae were not remarkable. The malpighian bodies appeared to be normal. The pulp cells and the venous sinuses were likewise not remarkable. A few large hemorrhagic areas were present as a part of the trauma to the external surface of the spleen. The blood vessels were not remarkable except for the vascular injuries in the hemorrhagic areas.

Chief Diagnosis.—Traumatic subcapsular laceration with hematoma of the spleen was the chief diagnosis.

Subsequent Course.—The postoperative course was uneventful. Roentgenologic examination showed a small collection of fluid in the left side of the chest, which could not be aspirated and which gradually absorbed. Secondary closure of the débrided wound of the chest was carried out successfully, and the patient was fully ambulatory within three weeks of operation. He was evacuated to the Zone of the Interior for disposition approximately six weeks after his admission to the hospital.

CASE 2.—A soldier, aged 38, sustained two perforating wounds of the chest at about 8 p. m., Aug. 15, 1944. He was given supportive therapy in the form of plasma, morphine and sulfadiazine at the battalion aid station about one-half hour after his injury. Penicillin therapy was begun at the clearing station. He was then evacuated to a hospital ship, where further supportive therapy, including transfusion of blood and administration of oxygen, was given. The chest was aspirated, and 700 cc. of blood was removed. The severity of the injuries was fully appreciated at this time, and it was felt that the patient's general condition would not permit operation. He arrived at this hospital at 6 p. m., Aug. 18, in poor condition.

Examination revealed four nondébrided small circular wounds. One was an entrance wound just below the left clavicle, anteriorly, with its exit in the left posterior wall of the chest, about 3 cm. lateral to the fourth dorsal vertebra. Another wound of entrance was at the left costal margin in the anterior axillary line, with its exit about 3 cm. to the right of the third lumbar vertebra.

There was complete sensory and motor loss below the level of the greater trochanters of the femurs. The upper part of the abdomen was rigid and tender, with the maximum rigidity and tenderness in the left upper quadrant. An indwelling urethral catheter was in place. The chest showed many coarse rales throughout, and the left side of the chest was dull to percussion in the lower half. The patient's blood pressure was 158 systolic and 90 diastolic; his temperature, 99.4 F.; his pulse rate,

100, and his respiratory rate, 32. A thoracentesis on the left side was done, and 175 cc. of blood was obtained. A hematocrit reading of 58 per cent, hemoglobin content of 19.6 Gm. and plasma protein level of 4.1 Gm. per hundred cubic centimeters, as determined by the Van Slyke copper sulfate method, were obtained on examination of a sample of the blood drawn from the chest. A sample of venous blood drawn at the same time and analyzed by the same method showed a hematocrit reading of 28 per cent, a hemoglobin content of 9.4 Gm. and a plasm protein level of 6.1 Gm. per hundred cubic centimeters. He was given oxygen by nasal administration and 1,000 cc. of whole blood. After neurologic consultation, it was decided that despite the patient's weakened condition, his only chance for survival depended on surgical intervention.

A preoperative diagnosis of perforating wounds in the upper part of the left lung and in the diaphragm, spleen and spinal canal was made. The possibility of other intra-abdominal injuries was entertained. The postoperative diagnosis was: perforating gunshot wound of the upper left part of the chest and the left lung; perforating gunshot wound of the left upper part of the abdomen, passing through the spleen, stomach, pancreas and spine at the level of the second lumbar vertebra.

Operation.—With the patient under endotracheally induced anesthesia a thoracotomy incision was made in the left lower part of the chest, and the thorax was opened through the ninth interspace. The lung was partially collapsed, and there was a large amount of blood in the pleural cavity. A small perforation through the apex of the lung was seen. The diaphragm, which was intact, was opened, and a small, adherent spleen with a laceration of the pedicle was found, together with a large amount of blood in the peritoneal cavity. The spleen was removed. The profuse bleeding continued, the blood seeming to come from the right upper part of the abdomen. The left and transverse parts of the colon were not perforated. The left lobe of the liver was uninjured. The lung was inflated, and a drainage tube was placed in the posterior costophrenic angle through the tenth interspace. The diaphragm was closed with running surgical sutures; the wall of the chest was closed with surgical catgut and silk sutures were used to close the skin.

The abdomen was prepared, and a long right upper rectus incision was made. The liver and the remainder of the colon were uninjured. Blood was coming profusely from the lesser curvature of the stomach. Exploration revealed a perforating wound through the midportion of the lesser curvature. There was also a perforation of the superior border of the pancreas. The perforations of the stomach were closed in two layers with fine surgical gut sutures. The gastrocolic ligament was opened, and the posterior wall of the stomach was examined; no further perforations were seen. No further bleeding was noted. Two soft Penrose drains were placed to the site of injury through the lesser sac, and the abdomen was closed in layers with chromic surgical gut and silk retention sutures. The immediate postoperative condition of the patient was poor. A second liter of blood was given during the operative procedure.

Pathologic Report.—Description of Tissue: The specimen consisted of a spleen measuring 9 by 7 by 3 cm. and weighing approximately 80 Gm. It was somewhat contracted, and the surface was wrinkled. There was evidence of bruising in the pedicle of the spleen.

Microscopic Observations: The capsule and trabeculae of the spleen were of normal architecture. The malpighian follicles were prominent. No evidences of inflammation or injury to the red and white pulp could be demonstrated. A considerable amount of pigment was scattered irregularly through the splenic tissue; most of this resembled artefacts from the solution of formaldehyde, but some of the clumps of brownish black pigment may have been hemosiderin.

Chief Diagnosis.—The diagnosis was traumatic injury to the pedicle of the spleen.

Subsequent Course.—The patient's convalescence was extremely stormy, being complicated by delirium tremens. He was completely irrational for about a week, but he gradually recovered, so that he was entirely rational by the tenth postoperative day. Pulmonary edema persisted for about five days. The thoracic drainage tube was removed in forty-eight hours. On September 1 the chest was clear, and the patient was rational. The wounds of the chest and abdomen were healed at this time except for a small pancreatic fistula, which showed evidence of closing.

The neurologist was of the opinion that a severe injury to the cauda equina had been sustained and that exploration at a later date was indicated.

Nutrition was maintained by the intravenous route for the first few days, after which fluids were tolerated orally. Whisky was given in an amount of 30 cc. three times a day for about twelve days. During the first twelve days in the hospital 4,500 cc. of blood and 500 cc. of plasma were given, together with sufficient dextrose and isotonic solution of sodium chloride to maintain a normal state of hydration. The use of an oxygen tent was of invaluable assistance for the first week. Penicillin therapy was continued, with a dose of 200,000 units daily, for nineteen days after the injury. Twenty-three days after the injury the left lung was completely reexpanded, and there was a slight drainage from the pancreatic fistula. There was some recovery of function in the abductor group of muscles of the left thigh, but urinary and fecal incontinence persisted, the former requiring an indwelling catheter.

On September 12 a laminectomy was performed, and the cauda equina was found to be almost completely destroyed at the level of the second lumbar vertebra. The patient's condition, so far as thoracic and abdominal injuries were concerned, was excellent at this time. The pancreatic fistula was closed.

Comment on the Case.—In this case, exposure was not adequate to visualize the wounds in the lesser curvature and in the pancreas. We feel that with further experience this area can be made available for inspection and therapy.

Case 3.—A soldier, aged 30, was injured at about 8 a. m., July 25, 1944, when he was thrown violently to the ground from a truck during an accident on the road. He was seen in this hospital about an hour later, at which time he was in shock and complained bitterly of abdominal pain. His blood pressure at this time was 130 systolic and 80 diastolic; the pulse rate, 160 and very feeble, and the temperature, 98.4 F. The hematocrit reading for venous blood was 30 per cent, the hemoglobin content 11.2 Gm. and the plasma protein level 6.3 Gm. per hundred cubic centimeters. The leukocyte count was 9,600, with a normal differential count. Malarial parasites (Plasmodium vivax) were seen in the blood smear. Significant observations on physical examination were exquisite tenderness and boardlike rigidity of the upper left side of the abdomen. Percussion of the abdomen revealed dulness throughout the left side and flank. The diagnosis of rupture of a malarial spleen was made, and the patient was prepared for operation by the administration of 1,500 cc. of whole blood, supplemented by 1,000 cc. during the operative procedure.

Operation.—A thoracotomy on the left side with the patient under endotracheally induced oxygen and ether anesthesia was made, and the chest was opened through the ninth interspace. There was no damage to the lung or diaphragm, but the base of the lung was firmly adherent to the diaphragm.

A large incision was made into the abdominal cavity through the diaphragm. A large amount of blood and clot was found within the abdominal cavity. The spleen, which was about three times its normal size, was bleeding profusely from a complete tear through the lower pole and several fractures near the hilus. The spleen was extremely friable and was attached in many places. It was freed from the surrounding structures, and the pedicle was clamped, divided and ligated with no. 2 chromic surgical gut. The stomach and colon were found to be normal. The diaphragm was closed in layers with 0 chromic surgical gut. The chest wall was closed in layers with 0 chromic surgical gut. One drain was placed into the chest at the posterior costophrenic angle and sealed under water. The immediate postoperative condition was good.

Pathologic Report.—Description of Tissue: The specimen consisted of a spleen measuring 20 by 16 by 5 cm. and weighing 600 Gm. The hilar surface showed a stellate tear with transcapsular rupture of the spleen. A small piece of spleen, measuring 4 by 5 by 2.5 cm., arrived separate—apparently it had been torn from the main substance of the spleen.

Microscopic Observations: Sections were composed of splenic tissue showing evidences of hemorrhage, particularly beneath the capsule in one area. The malpighian follicles appeared to be increased in number and size. An increase of the reticuloendothelial cells was present both in the follicles and in the sinuses. A large number of reddish brown pigmented cells were present. Impression smears of the fresh splenic tissue stained with Wright's stain revealed the presence of P. vivax.

Chief Diagnosis.—The injury was diagnosed as transcapsular rupture of a malarial spleen.

Subsequent Course.—A duodenal tube was used for twenty-four hours and 1,000 cc. of blood was given to the patient on the first postoperative day. He was given a full diet on the third postoperative day. The intercostal catheter was removed on the fifth day, and the patient was out of bed on the eighth day. Active antimalarial therapy was carried out during convalescence, and a blood smear was negative for parasites when the patient was transferred to an Italian hospital, on the tenth day, for further convalescence.

COMMENT

This was our first experience with the transthoracic route for an injury known to involve exclusively an intra-abdominal organ. This approach was chosen deliberately, and we feel the choice to be justified both by the ease of removal and by the smooth and rapid convalescence. It was the operator's opinion that the use of an abdominal incision would have made splenectomy more difficult. Before the war we witnessed the removal of malarial spleens by the abdominal route and were impressed by the difficulties encountered. It is also of interest that the diagnosis of malarial involvement of the spleen was made preoperatively.

EARLY EFFECTS ON DOGS OF SECTION OF THE EIGHTH CERVICAL SEGMENT OF THE SPINAL CORD AND THEIR BEARING ON SHOCK

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Since it has been considered that nervous factors may play an important part in the production of surgical shock by lowering the blood pressure and impairing the circulation, it should be of interest to study the physiologic, morphologic and biochemical reactions in animals in which the blood pressure is lowered by the alteration in nervous function which follows section of the eighth cervical segment of the spinal cord. The most immediate general effects are motor and sensory paralysis distal to the level of section and vasomotor paralysis, complete except for the vasodilator fibers to the chorda tympani and glossopharyngeal nerves and the antidromic pathways of the posterior roots of the cervical nerves. After a brief initial rise there follows a marked fall of blood pressure, a slowing of the pulse and respiration, a fall of body temperature and a variable degree of depression or stupor, which usually wears off within twenty-four hours. The excitability of all somatic, vascular and visceral reflexes posterior to the section is diminished. This early state of the animal was defined by Sherrington as spinal shock.

The most widely accepted theory as to the cause of the fall in blood pressure following section of the spinal cord at the eighth cervical vertebra is that interruption of the pathways to the sympathetic nervous system cuts off vasoconstrictor impulses coming from the higher centers.[1] Diminution of respiratory movements by paralysis of the intercostal muscles and of intra-abdominal tension by paralysis of the muscles of the abdominal wall contributes somewhat to the hypotension. It has also been maintained[2] that the flaccid paralysis of skeletal muscles from interruption of motor pathways results in dilatation of capillaries, venules and veins and that the subsequent pooling of blood from lack of extravascular muscular support is an important contributing factor in lowering blood pressure and impairing the general circulation. This theory is contradicted by the decided fall in blood pressure which results from inhibition of the vasoconstrictors produced by stimulation of the depressor nerves[3] and there is still doubt as to the degree of its importance.

EXPERIMENTAL PROCEDURES AND METHODS

Studies of the postoperative circulatory effects of section of the eighth cervical segment of the spinal cord were made, a different type of experimental procedure being used on each of two groups of dogs. In both groups the picture of spinal shock developed soon after section of the cord. In group 1 the animals were kept on the operating table throughout the experiment, a femoral artery was connected with a mercury manometer for continuous recording of blood pressure, fluids and food were withheld and samples of blood were taken at varying intervals. These animals passed from spinal shock into a state of exhaustion, with failure of the circulation and urinary suppression, and died. In group 2 all extraneous influences were reduced during the acute phase to as nearly a minimum as possible, which protected against circulatory failure and favored recovery of the animals. They were not restrained, were kept warm and were given intravenous injections of isotonic solution of sodium chloride, food, drink and nursing care. The experimental procedures in the two groups were as follows:

Group 1.—There were 7 dogs in this group. Cannulation of the femoral arteries was carried out with the animal under anesthesia (evipal sodium, 40 mg. per kilogram of body weight). A glass cannula in the left femoral artery was connected to a mercury manometer for recording of blood pressure. Isotonic solution of sodium chloride was used in the system, and heparin was injected into the cannula bulb to prevent clotting.

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To facilitate the withdrawal and replacement of blood samples in the face of the low blood pressure following section of the cord, a small metal cannula was placed in the right femoral artery. When not in use, it was stoppered with a small cork. Aseptic section of the eight cervical segment of the spinal cord was then performed, with the animal under evipal sodium anesthesia in 4 cases and under ether anesthesia in 3, with no appreciable difference in the after-effects on the blood pressure. Loss of blood from the surgical procedures was relatively slight (under 50 cc.) except in 1 case, in which the animal was given a replacement transfusion. After section of the cord the animals were kept on their backs and the blood and circulatory changes followed until death occurred.

Analyses were made from 45 cc. samples of blood withdrawn from the right femoral artery. Immediate volume for volume replacement was made by a transfusion of heparinized blood from a donor animal. Samples were taken immediately before section of the cord, at the first, third, sixth and twelfth and twentieth to twenty-third hours and at six hour intervals thereafter for as long as the animals survived. Approximately 30 cc. of the arterial blood was collected under oil for serum analyses. Ten cubic centimeters was defibrinated for whole blood analyses; 5 cc. was heparinized for oxygen determinations and 1 cc. was heparinized for red blood cell, hematocrit and hemoglobin determinations. Serum analyses were made for water, total carbon dioxide, chloride, sodium, potassium, calcium, magnesium and proteins; whole blood analyses, for oxygen, cell volume, water, chloride, sodium and potassium. In addition to the blood analyses, tissue analyses were made on muscle from dogs 202 and 211 and on muscle, skin and liver obtained from dog 239 just before it was killed, twenty-eight and one-half hours after section of the cord. The chemical methods and procedures used were those employed in previous studies by one of us.[4]

Blood volume studies were made on 1 dog in the group—dog 239. Necropsy was performed on all animals, and specimens for microscopic section of tissues were obtained.

Group 2.—There were 5 dogs in this group. With the animal under evipal sodium anesthesia (40 mg. per kilogram of body weight) and with aseptic technic, the spinal cord was sectioned at the eighth cervical segment and the wound sutured. Postoperatively isotonic solution of three chlorides containing 10 per cent dextrose was given intravenously, and most animals ate voluntarily the next morning. Gavage of milk and eggs and intravenous injections of 10 per cent dextrose in isotonic solution of three chlorides were frequently resorted to during the early postoperative period in order to provide an adequate intake of food. The total daily fluid intake was kept up to 40 to 50 cc. per kilogram of body weight. The urinary bladder was emptied by suprapubic compression. Blood pressures were determined by puncture of an unexposed femoral artery with a needle attached to a Kaufman syringe which was connected to a mercury manometer.

Samples of blood for this group were withdrawn, replaced and analyzed in the same amounts as in group 1. By attaching a three way stopcock to the Kaufman syringe, it was possible to read the blood pressure, withdraw the sample and transfuse blood through the same needle with but one puncture. Studies both of blood pressure and of blood were made on 3 of the 5 dogs; the remaining 2 were followed for pressure studies only. Routine determinations of pressure and samples of blood were taken preoperatively, three hours after section, each morning for the succeeding four days and then at progressively longer intervals thereafter. Samples for blood volume studies, by the standard Evans blue dye method, were taken by direct punctures of the saphenous vein.

The studies made in the course of the experiments on this group are divided into two sections, as the animals were allowed to survive over periods ranging from thirteen to one hundred and nineteen days. The first section covers the period of acute reaction from division of the cord, which usually lasts from four to six days, and is reported on here. The second section covers the remaining period of gradual recovery until the time of killing the animal and will be reported on later.

RESULTS OF EXPERIMENTS

Group 1.—In evaluating the results of experiments on this group, the animals are divided into two series: series A, including those in which the bowel was free from changes, and series B, including those in which there had been hemorrhagic exudation into the lumen of the bowel. The two series are considered jointly.

Blood Pressure: When the cord was sectioned, the blood pressure suddenly rose and fell and

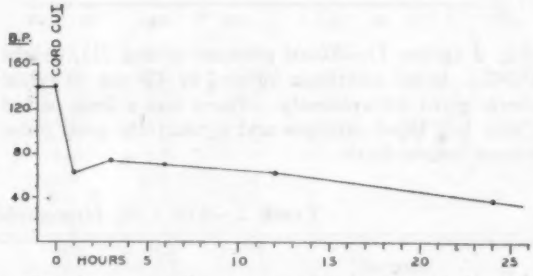

Fig. 1 (group 1).—A composite curve of the blood pressures of 7 dogs for twenty-four hours following section of the spinal cord at the eighth cervical vertebra.

then declined gradually to 60 to 80 mm. of mercury within one to one and one-half hours. The pressure then usually fluctuated, first at a higher level and then in the vicinity of 60 to 80 mm. of mercury for periods of six to twelve hours, after which it gradually declined until death occurred, from twenty-four to thirty-three and one-third hours after section. A composite curve of the pressures of the 7 dogs for twenty-four hours is shown in chart 1, while individual pressures taken at intervals are shown in table 1. In 4 of the 7 animals, blood was found in the intestinal lumen at necropsy, and the blood pressures of these animals were lower than those of the rest of the group. In some cases the blood pressure was maintained at very low levels for long periods before circulatory failure finally occurred. This is well illustrated in chart 2, which is a condensed

4. (*a*) Eichelberger, L.: J. Biol. Chem. **128**:137, 1939. (*b*) Eichelberger, L., and Bibler, W. G.: ibid. **132**:645, 1940. (*c*) Eichelberger, L.; Eisele, C. W., and Wertzler, D.: ibid. **151**:177, 1943.

drawing of the graph for a representative animal. The pulse pressure of this animal was also relatively well maintained.

The pulse rate, which averaged 132 per minute before section of the cord, changed relatively little during the day of operation, but by the twenty-first hour after section it had declined to an average of 70 per minute, and then it went to still lower levels before death occurred. The respirations declined more rapidly to the vicinity of 50 per cent of the early postoperative rate and were usually somewhat labored. With but 1 exception, there was a pronounced fall of temperature, the greatest drop being to 78 F. For three to six hours after section of the cord the animals remained in a quiet stupor, after which they were more alert and moved the forelegs and head. By the following morning they had usually lost consciousness, which was never regained. The urinary secretion was reduced in varying degrees, as shown by the observations at necropsy. The bladder had not been emptied during the course of the experiments.

TABLE 1.—*Blood Pressure Studies, Group 1*

Experiment No.	Survival After Cord Section, Hr.	Initial Blood Pressure, Mm. Hg	Blood Pressure Levels After Cord Section, Mm. Hg				
			1 to 3 Hr.	3 to 6 Hr.	6 to 9 Hr.	9 to 12 Hr.	21 to 26 Hr.
Series A.—No Blood in Lumen of Bowel							
239	28.5	120	80	90	80	75	55
221	28.5	160	70	65	65	60	45
202	33.2	130	60	90	90	90	70
Series B.—Leakage of Blood and Plasma into Lumen of Bowel							
230	24.0	170	50	60	60	50	26
211	25.5	160	50	80	60	40	22
198	27.8	110	60	70	70	50	40
201	33.3	130	76	76	70	70	60

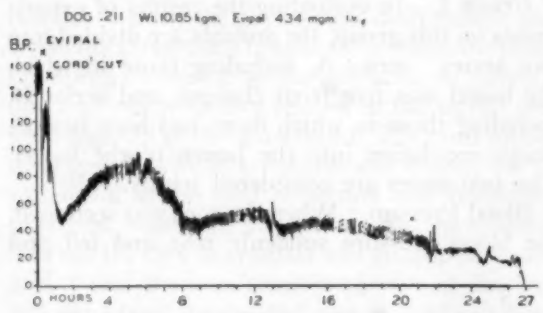

Fig. 2 (group 1).—Blood pressure of dog 211, weight 10.85 Kg., under anesthesia induced by 434 mg. of evipal sodium, given intravenously. There was a long period of very low blood pressure and a relatively good pulse pressure before death.

Red Cell, Hemoglobin and Hematocrit Determinations: These determinations were made at intervals, as shown in table 2. One hour after section of the cord there was a moderate to severe hemodilution in all cases. Subsequent determinations revealed slight to moderate fluctuations for the next eleven hours, after which there was a trend toward hemoconcentration, most evident in the animals of series B, in which hemorrhage into the bowel had occurred.

TABLE 2.—*Red Cell, Hemoglobin and Hematocrit Studies, Group 1*

Experiment No.	Survival After Cord Section, Hr.		Control Sample	Time of Sample After Cord Section, Hr.						
				1	3	6	12	20 to 23	25 to 29	32 to 33
Series A.—No Blood in Lumen of Bowel										
239	28.5	Red blood cells, millions	8.00	6.36	5.62	5.62	6.12	6.18	6.30	....
		Hemoglobin, Gm.	16.6	14.0	12.4	12.3	12.7	12.7	13.0	
		Hematocrit, per cent	52.5	41.5	37.5	37.0	35.0	39.0	38.5	
221	28.5	Red blood cells, millions	8.08	6.96	6.24	6.66	6.90	7.10	7.40	....
		Hemoglobin, Gm.	16.9	14.8	14.5	14.4	15.0	15.0	15.2	
		Hematocrit, per cent	52.5	46.5	42.5	43.0	45.0	47.0	47.0	
202	33.2	Red blood cells, millions	7.46	6.02	5.86	6.04	6.52	5.72	5.70	5.20
		Hemoglobin, Gm.	14.8	13.5	13.5	13.8	14.2	12.8	12.4	11.4
		Hematocrit, per cent	43.0	38.0	38.0	39.0	42.0	38.0	36.0	34.0
Series B.—Leakage of Blood and Plasma into Lumen of Bowel										
230	24.0	Red blood cells, millions	7.12	5.58	5.80	5.69	6.06	8.70	....	....
		Hemoglobin, Gm.	16.9	13.5	13.5	13.5	14.8	17.4		
		Hematocrit, per cent	48.0	42.0	40.0	40.5	43.5	44.0		
211	25.5	Red blood cells, millions	8.42	7.20	7.12	7.28	7.92	8.88	9.82	....
		Hemoglobin, Gm.	13.0	11.6	11.5	14.2	18.0	18.5	20.0	
		Hematocrit, per cent	56.5	52.0	52.0	53.5	57.0	61.5	67.0	
198	27.8	Red blood cells, millions	9.60	7.76	7.16	7.76	9.36	9.20	8.58	....
		Hemoglobin, Gm.	17.4	14.4	13.9	15.2	17.1	17.3	21.0	
		Hematocrit, per cent	57.0	40.5	41.5	45.0	51.0	52.0	59.0	
201	33.3	Red blood cells, millions	8.56	7.74	6.88	5.50	7.02	7.92	8.96	10.72
		Hemoglobin, Gm.	17.8	16.8	15.6	13.2	16.3	18.0	20.0	21.2
		Hematocrit, per cent	50.0	46.5	42.0	41.0	46.5	49.0	56.0	61.5

Blood Volume Studies: Studies of blood volume were made only for dog 239. The results are shown in table 8 and discussed in connection with those of group 2.

TABLE 3.—*Changes in Red Cell Volume and Oxygen Content (in per Cent of the Control Values) of Whole Blood from Representative Dogs of Group 1*

Experiment No.	Sample No.	Time After Section, Hr.	Cell Volume, %	O_2 Content, mM/Liter of Blood	Cell Volume, Δ %	O_2 Content, Δ %
239 (Series A)	Control	0	52.5	9.18		
	2	1	....	....	—21.2	—20.4
	3	3	....	....	—28.2	—22.7
	4	6	....	....	—29.9	—23.1
	5	12	....	....	—33.3	—16.1
	6	22.5	....	....	—25.7	—24.4
	7	28.5	....	....	—26.3	—23.7
230 (Series B)	Control	0	47.8	8.91		
	2	1	....	....	—11.9	+ 2.7
	3	3	....	....	—15.9	—11.7
	4	6	....	....	—14.8	— 9.8
	5	12	....	....	— 9.2	.....
	6	23	....	....	— 7.7	+10.3

control values with those following the cutting of the cord, the results have been expressed in per cent change of the original concentration (ΔH_2O, Δ Cl, etc.). The concentration of water and electrolytes in the red cells was calculated from the analysis of whole blood. When the values obtained after cutting of the cord are compared with the control values, the most significant differences found are the lowered serum protein and carbon dioxide content and the decreases in the cell volume and oxygen content.

In table 5 the analyses of skeletal muscle, liver and skin from dog 239 are given. It is noteworthy that the total water content of the tissues analyzed did not decrease but remained within limits of normal values. In the muscle, there was a decrease in the extracellular fluids associated with a swelling of the muscle cells. This is an instance of dehydration in the sense that the extracellular phase has been diminished. The

TABLE 4.—*Changes in Water, Electrolytes and Protein Concentrations (in per Cent of the Control Values) in the Serum and Erythrocytes of Two Representative Dogs from Series A and B of Group 1 Following Experimental Section of the Spinal Cord*

Values are expressed in units per liter.

Experiment No.	Sample No.	Time After Section, Hr.	Serum or Cells	p_H	Total CO_2, mM	H_2O, Gm.	Cl, mM	Na, mM	K, mM	Ca, mM	Mg, mM	Total Protein, Gm.
239, Series A	Control	0	Serum	7.38	15.67	932.6	114.1	141.5	3.67	2.65	1.08	61.1
				±	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ%	Δ %
	2	1		—	+14.12	+0.41	+1.23	+0.21	—7.36	+6.79	—8.74	—11.61
	3	3		—	+20.83	+1.19	+0.09	—1.90	—7.36	+11.33	—3.89	—9.66
	4	6		—	+26.20	+1.17	—2.28	—4.44	—15.80	+5.66	+2.91	—9.17
	5	12		—	+17.88	+0.83	—2.72	—4.72	—14.45	+9.44	+11.65	—11.61
	6	22.5		+0.05	+ 8.17	+0.89	—2.72	—3.46	—13.07	+13.96	+21.39	—13.25
	7	28.5		—0.01	— 5.05	+0.27	—2.28	—4.72	—3.0	+22.65	+23.30	—16.35
						Gm.	mM	mM	mM			
	Control	0	Erythrocytes	.....	.....	729.0	69.4	103.3	9.03			
						Δ %	Δ %	Δ %	Δ %			
	2	1		.....	.....	—2.33	—38.4	—18.3	—12.5			
	3	3		.....	.....	—3.71	—12.8	— 3.2	—15.8			
	4	6		.....	.....	—2.61	—17.0	— 9.8	+20.5			
	5	12		.....	.....	—0.96	—17.0	— 4.8	+11.3			
	6	22.5		.....	.....	—1.65	—11.5	—20.3	—11.0			
	7	28.5		.....	.....	—0.96	—18.0	—22.2	—10.2			
				p_H	mM	Gm.	mM	mM	mM	mM	mM	Gm.
230, Series B	Control	0	Serum	7.40	—	935.7	110.7	147.7	3.82	2.66	0.90	63.2
	2	1		....	21.33	.....						
				Δ ±	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ%	Δ %
	2	1		—0.06	—	+1.10	+3.16	—2.98	+4.19	—	—	—11.55
	3	3		+0.02	+10.02	+1.20	+2.53	—3.66	—11.00	—	—	—15.20
	4	6		—	—	+0.95	+2.26	—4.34	+19.37	—	—	—17.55
	5	12		—	—	+0.97	+0.45	—3.18	+42.4	—	—	—10.29
	6	23		+0.02	—	+0.50	+1.36	—4.81	+59.7	—	—	— 6.05
						Gm.	mM	mM	mM			
	Control	0	Erythrocytes	.....	.....	710.2	65.7	101.7	10.47			
						Δ %	Δ %	Δ %	Δ %			
	2	1		.....	.....	—0.80	+1.50	—19.38	+1.60			
	3	3		.....	.....	+1.00	—8.40	—1.48	+3.10			
	4	6		.....	.....	—2.82	+0.15	+13.09	+8.00			
	5	12		.....	.....	—0.31	—3.45	—9.54	+4.33			
	6	23		.....	.....	—5.44	—16.20	—15.95	+10.05			

Electrolyte, Water and Protein Content of Serum, Erythrocytes and Tissues: In tables 3, 4 and 5 are presented the values in detail of electrolyte, water and protein content of serum, erythrocytes and tissues for 2 representative dogs of this group. To facilitate comparison of the

circulatory space, as determined by hemoglobin methods in the muscle, was 92 cc. per kilogram, which is more than the mean average value of 71 cc. for muscle from normal dogs. This may indicate either a trapping of erythrocytes in the tissue or else a sluggish flowing of blood into

the many dilated capillaries. In the liver, there was an increase in the concentration of chloride, in an amount indicating an increase of 90 Gm. in the extracellular phase per kilogram of liver. In the skin, the values for chloride and sodium indicated that there had been a decrease in the extracellular fluid volumes. At the same time, the water from the cells of the skin shifted out of the cells into the extracellular spaces, apparently because of the potassium concentration. Since skin is a reservoir capable of holding large amounts of sodium, chloride and water for the body, it is not surprising that the skin gives up a large percentage of its original sodium and lesser degree, in other viscera. Leukocytic infiltration of the damaged visceral areas was also common. In dogs 198 and 230 a beginning bronchopneumonia was present. The heart and skeletal muscles showed little change. In 4 dogs there were congestion and surface necrosis of the villi of the upper part of the intestine and loss of considerable amounts of blood and plasma into the lumen, similar to the changes reported by Brooks and Blalock [5] in shock produced by hemorrhage.

Group 2.—Blood Pressure: The results during the first several hours of the acute phase were similar to those in group 1, but from that

TABLE 5.—*Water and Electrolyte Content of Tissues, Dog 239, Group 1*

Values are given in units per kilogram of blood-free, fat-free tissue.

Tissue	H_2O, Gm.	Cl, mM	Na, mM	K, mM	N, Gm.	Blood, Cc.	(F),* Gm.	$(H_2O)c$,† Gm.	S,‡ Gm.	Intracellular K, mM
Muscle (rectus abdominis)...	776.8	15.82	21.93	86.0	....	92	128	649	223	85.6
Liver.....	773.2	37.34	37.45	74.1	....	76	301	472	227	73.0
Skin.....	716.4	76.3	76.7	28.15	45.4					
Mean Normal Values §										
Muscle.....	775	18.4	29.1	98.4	....	71	154	621	225	96.6
Liver.....	758	33.1	39.5	73.2	....	196	211	547	242	74.3
Skin.....	708	86.7	96.5	22.5	46.8					

* Extracellular phase.
† Intracellular phase.
‡ Solids of intracellular phase.
§ Muscle (Childs, A., and Eichelberger, L.: Am. J. Physiol. **137**: 384, 1942); liver (Eichelberger, L.: J. Biol. Chem. **138**: 583, 1941); skin.[4c]

TABLE 6.—*Blood Pressures, Pulse Rate, Respiratory Rate and Rectal Temperatures of Group 2 Taken During the Acute Phase Following Section of the Spinal Cord*

Interval Following Cord Section, Days	234				237				238				232			
	Blood Pressure	Pulse	Respiration	Temperature, F.	Blood Pressure	Pulse	Respiration	Temperature, F.	Blood Pressure	Pulse	Respiration	Temperature, F.	Blood Pressure	Pulse	Respiration	Temperature, F.
Control	140	100	32	...	130	72	28	101.8	170	76	28	100.0	140	..	..	....
0.13	70	120	40	99	80	68	14	91.0	58	76	16	90.0	74	88	16	98.8
1.0	80	100	24	100	68	84	16	100.0	60	80	18	92.5	60	84	15	98.4
2.0	70	88	22	102	80	84	18	101.0	64	76	17	100.0				
3.0	72	86	24	102	68	84	18	101.5	80	92	24	100.5	Killed for studies of tissue			
4.0	73	84	34	103	80	88	16	101.0	80	88	20	100.5				

chloride content to help maintain the vascular system as nearly normal as possible.

Observations at Necropsy: The obvious gross changes were congestion of the liver, spleen and kidneys and of the dependent portions of the lungs and a moderate inflammatory reaction in the wound at the site of cannulation of each femoral artery. There was a noticeable reduction in the output of urine. The amounts in the bladder varied from 20 to 325 cc. and were in direct proportion to the blood pressure levels maintained throughout the experiments.

Microscopically, there were varying degrees of passive congestion of the viscera, especially of the lungs, liver and kidneys, and acute degenerative changes in the parenchymatous cells of the same organs, as well as in the adrenals, and, to

point forward the animals held their own and in no case did surgical shock develop. The changes in blood pressure, pulse rate, respiratory rate and temperature in 3 of the 5 animals are shown in table 6. After the initial quick rise and fall, the blood pressure gradually declined to 60 to 80 mm. of mercury in one to three hours and fluctuated about that critical level for from four to six days. The readings for the first one hundred hours are shown graphically in chart 3. The pulse remained regular and showed relatively little variation in rate. The respirations were retarded in frequency on nearly all counts throughout the period. The fall in temperature

5. Brooks, B., and Blalock, A.: Ann. Surg. **100**: 178, 1934.

was confined almost entirely to the first twenty-four hours and in some cases was marked for portions of that period. Despite the fact that the blood pressure throughout the four to six day period fluctuated along the borderline at which anuria and surgical shock might develop, the urinary output and the general circulation remained fairly adequate, the general condition of the animals slowly improved and they went on to survival.

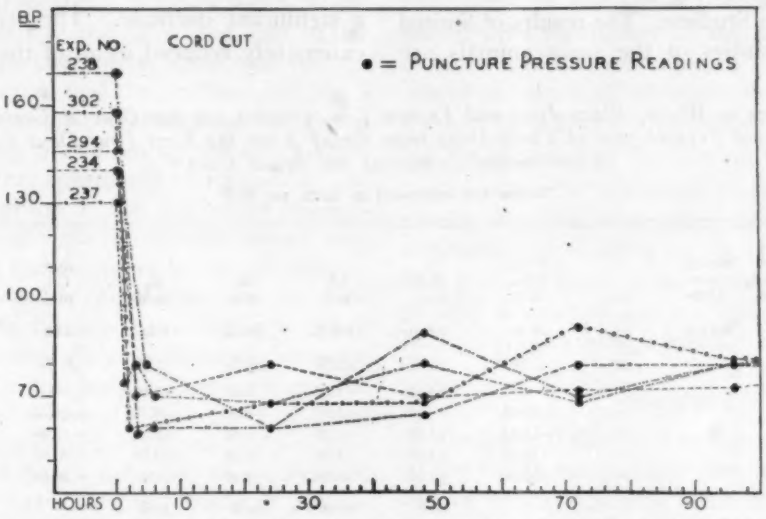

Fig. 3 (group 2).—Blood pressures for ninety-six hours of 5 dogs surviving section of the spinal cord at the eighth cervical vertebra.

TABLE 7.—*Red Cell, Hemoglobin and Hematocrit Studies on Group 2 Made During the Acute Phase Following Section of the Spinal Cord*

Experiment No.	Time of Killing After Cord Section	Determination	Control	Time in Days of Sample After Cord Section 1/8	1	2	3	4
234	119 days	Red blood cells, millions	9.02	7.30	5.78	5.20	4.94	4.67
		Hemoglobin, Gm.	18.1	14.1	12.2	10.7	10.3	9.8
		Hematocrit, per cent	53.7	43.2	37.2	32.9	31.9	28.5
237	39 days	Red blood cells, millions	7.32	6.26	5.54	4.84	4.64	5.10
		Hemoglobin, Gm.	18.0	15.1	12.5	11.2	10.2	12.3
		Hematocrit, per cent	50.9	41.0	36.5	34.4	29.7	31.6
238	13 days	Red blood cells, millions	5.70	4.40	4.08	4.18	4.22	3.50
		Hemoglobin, Gm.	13.6	10.1	9.4	9.6	9.8	8.3
		Hematocrit, per cent	36.6	30.8	27.0	26.5	27.9	25.2
232	29 hr.	Red blood cells, millions	7.20	6.44	6.24	Killed for tissue studies		
		Hemoglobin, Gm.	14.0	12.7	12.6			
		Hematocrit, per cent	40.0	35.8	33.0			

TABLE 8.—*Blood Volumes by Evans Blue Dye Method on Dogs Subjected to Spinal Cord Section at the Eighth Cervical Vertebra*

Experiment No.	Weight, Kg.	Determination	Controls 24 Hr. Before Section	After Section of Cord 3 to 4.5 Hr.	25 to 30 Hr.	75 Hr.
234	8.9	Plasma vol., cc.	360	395	...	530
		Total vol., cc.	855	675	...	730
		R. C. M., cc.	495	280	...	200
		Hematocrit, %	57.5	42.0	...	27.0
237	14.0	Plasma vol., cc.	655	668	...	816
		Total vol., cc.	1,393	1,103	...	1,150
		R. C. M., cc.	738	435	...	334
		Hematocrit, %	53.0	39.5	...	29.0
238	11.4	Plasma vol., cc.	600	632	...	518
		Total vol., cc.	1,092	902	...	720
		R. C. M., cc.	492	270	...	202
		Hematocrit, %	45.0	30.0	...	28.0
232	9.2	Plasma vol., cc.	495	525	480	
		Total vol., cc.	990	820	780	
		R. C. M., cc.	495	295	300	
		Hematocrit, %	50.0	36.0	39.0	
				6.5 Hr.		
239	13.6	Plasma vol., cc.	744	600		
		Total vol., cc.	1,548	945		
		R. C. M., cc.	804	345		
		Hematocrit, %	52.0	36.5		

TABLE 9.—*Changes in Red Cell Volume and Oxygen Content (in per Cent of the Control Values) of Whole Blood from Dogs of Group 2*

Experiment No.	Sample No.	Time After Section, Days	Cell Volume, %	O_2 Content, mM/Liter of Blood	Cell Volume %	O_2 Content, %
234	Control	0	53.7	10.24		
	2	0.13	....	.....	—19.5	—19.1
	3	1	....	.....	—30.7	—36.5
	4	2	....	.....	—38.8	—36.7
	5	3	....	.....	—40.6	—26.1
	6	4	....	.....	—47.0	—43.1
237	Control	0	50.9	9.40		
	2	0.13	....	....	—19.4	—14.05
	3	1	....	....	—28.3	—21.28
	4	2	....	....	—32.4	—28.70
	5	3	....	....	—41.6	—41.20
	6	4	....	....	—37.9	—35.30
238	Control	0	36.6	7.66		
	2	0.13	....	....	—15.8	—20.22
	3	1	....	....	—26.2	—12.54
	4	2	....	....	—27.6	—10.44
	5	3	....	....	—23.8	—31.70
	6	4	....	....	—31.1	—36.40

Red cell, hemoglobin and hematocrit determinations on 3 dogs are shown in table 7. They revealed a sharp decline in all three values three hours after section of the cord. Subsequent determinations showed a further slight to moderate decline for the following days.

Blood Volume Studies: The results of limited blood volume studies of the same animals are shown in table 8. In all the experiments, the plasma volume at three to four and one-half hours after section of the cord was in the vicinity of the control level. At the end of seventy-five hours 2 dogs showed significant increases and 1 a significant decrease. The red cell mass was extensively reduced in all of the analyses.

TABLE 10.—*Changes in Water, Electrolytes and Protein Concentration (in per Cent of Control Values) in the Serum and Erythrocytes of Three Dogs from Group 2 for the First Four Days Following Experimental Section of the Spinal Cord**

Values are expressed in units per liter.

Experiment No.	Sample No.	Time After Section, Days	Serum or Cells	p_H	Total CO_2, mM	H_2O, Gm.	Cl, mM	Na, mM	K, mM	Ca, mM	Mg, mM	Total Protein, Gm.
234	Control	0	Serum	—	24.40	932.0	104.3	141.2	4.14	3.02	1.02	61.4
				±	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %
	2	0.13		—	— 4.87	+0.53	+2.06	—3.47	+5.07	—	—	— 8.30
	3	1		—	—19.44	+1.82	+1.87	—5.95	—7.73	—18.55	+ 4.90	— 4.73
	4	2		—	—14.44	+1.18	+2.25	—4.04	+3.62	—19.88	+18.62	—12.38
	5	3		—	—18.15	+1.29	+4.13	—3.33	+14.00	—20.88	— 0.98	—17.10
	6	4		—	—13.20	+1.18	+2.06	—3.40	+2.66	—26.50	+ 0.86	—26.55
						Gm.	mM	mM	mM			
	Control	0	Erythrocytes	.....	.....	708.0	54.0	98.0	5.83			
						Δ %	Δ %	Δ %	Δ %			
	2	0.13		.....	.....	+1.28	—0.18	+6.12	+19.05			
	3	1		.....	.....	+5.41	+2.04	—5.10	+66.0			
	4	2		.....	.....	—4.96	—7.04	—10.63	+62.8			
	5	3		.....	.....	+3.12	—10.20	+2.04	+61.6			
	6	4		.....	.....	±0	—12.95	—4.80	+66.0			
					mM	Gm.	mM	mM	mM	mM	mM	Gm.
237	Control	0	Serum	7.47	20.30	939.8	114.4	142.7	4.57	2.44	0.89	54.8
				±	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %
	2	0.13		—0.05	— 6.65	+0.98	+4.64	—0.63	—16.2	— 4.10	+11.25	— 3.3
	3	1		+0.08	—28.40	+0.53	—0.18	—1.54	— 3.28	— 7.38	+23.05	— 7.3
	4	2		+0.01	— 6.50	+1.32	+0.35	—3.78	+12.05	—15.58	± 0	—20.2
	5	3		+0.03	— 2.96	+0.41	+1.58	—1.89	+11.80	—16.40	—29.20	—12.9
	6	4		—0.04	+ 4.63	+0.85	—4.46	—4.91	+17.73	—14.75	—29.20	—16.0
						Gm.	mM	mM	mM			
	Control	0	Erythrocytes	.....	.....	822.7	85.6	114.0	7.98			
						Δ %	Δ %	Δ %	Δ %			
	2	0.13		.....	.....	+2.53	—4.09	+6.18	—2.63			
	3	1		.....	.....	+4.59	+9.11	+6.05	—8.56			
	4	2		.....	.....	+4.46	+9.11	+5.19	—15.90			
	5	3		.....	.....	+6.73	+13.08	+9.88	—6.64			
	6	4		.....	.....	+5.43	+5.36	+2.64	—1.25			
					mM	Gm.	mM	mM	mM	mM	mM	Gm.
238	Control	0	Serum	7.38	17.55	931.9	115.5	141.8	3.83	2.25	1.07	57.2
				±	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %
	2	0.13		+0.04	—14.15	+1.40	+3.29	+1.39	—7.04	+ 9.78	+18.7	—11.90
	3	1		+0.07	—10.76	+1.35	—3.08	+4.52	±0	+ 6.22	+ 5.61	—12.40
	4	2		±0	—13.40	+1.80	+5.64	+3.97	+5.48	— 5.34	+ 3.74	—22.90
	5	3		±0	—20.10	+1.64	+2.60	—4.31	—19.60	—11.10	+19.6	—23.09
	6	4		+0.11	+15.90	+1.72	—3.64	—2.71	+13.85	+10.21	—	—20.10
						Gm.	mM	mM	mM			
	Control	0	Erythrocytes	.....	.....	696.0	58.0	100.3	11.96			
						Δ %	Δ %	Δ %	Δ %			
	2	0.13		.....	.....	+1.82	+5.68	+0.40	+23.75			
	3	1		.....	.....	+1.41	+64.6	+2.89	+21.00			
	4	2		.....	.....	+0.14	+9.30	—13.05	+22.65			
	5	3		.....	.....	+2.82	+13.10	—12.45	+23.10			
	6	4		.....	.....	+3.24	+9.48	+25.80	—12.38			

In dog 239, group 1, at the end of six and one-half hours, the extreme reduction of red cell mass was accompanied with a less noticeable reduction in plasma volume.

Electrolyte, Water and Protein Content of Serum and Erythrocytes: In tables 9 and 10 are presented the analytic and calculated data in detail relating to the electrolyte, water and protein content of the serum and the erythrocytes for 3 representative experiments from the second group of animals. Since the values for the two groups are similar, they are considered here together. In group 2, as in group 1, the significant changes found in the blood were the lowered serum protein content and the decreases in the cell volume and oxygen content. These alterations indicate hemodilution, which might have been a result of the entrance of extracellular or intracellular water from elsewhere in the body. They were not the result of extensive loss of blood during section of the cord. The plasma volume was not increased for a number of hours following the operation, which suggests that interstitial fluid had not entered the circulating system. This deviation may be a result of either the trapping of red cells or the collapsing of blood vessels because of the prevailing low blood pressure, large numbers of red cells being retained thereby, as evidenced by a greatly decreased cell volume. Such action would be expected to decrease the original blood volume. This was verified experimentally. If interstitial fluid had entered the now decreased vascular system, the tissues of the body should have become dehydrated. On the contrary, skeletal muscle, liver and skin did not change in total water content. Even if some interstitial fluid did enter the vascular system, it was not enough to account for the lessened proteins; therefore, the most likely way to account for this change was that some protein must have been lost through the vascular membranes. It is to be noted that the serum water values never decreased very much. In a number of animals the serum water increased from 1 to 2 per cent and was accompanied with a loss of water from the red cells, which were attempting to restore osmotic equilibrium.

In all experiments the changes in serum sodium and chloride concentrations were small. This observation holds for the red cells, too, except for dog 239, in group 1, in which the cell chloride and sodium concentrations decreased sharply. The decrease in chloride could result in part from the low carbon dioxide tension existing in the serum of this animal. The chloride was not decreased from excretion in the urine, since oliguria was present.

The data for serum potassium from all animals in group 2 and series B of group 1 showed a decided rise. The dogs of series A, group 1, showed a decrease in the values for potassium. The highest concentration of serum potassium was found in the animals in which blood had leaked into the lumen of the intestine. In no instance was the potassium of such a concentration as to have toxic effects on the heart, although it might have been a contributing factor in retarding the recovery of the animals in group 2.

The values for calcium of the serum of all dogs, except dog 239, were lower after the cutting of the cord, compensating for the change in the protein level, as total calcium must vary with total protein if calcium ion concentrations are to be held within physiologic limits.

COMMENT

The general effects of section of the spinal cord at the eighth cervical segment for the first six to twelve hours were the same in both groups of experiments. In group 1 the further decline of blood pressure and the failure of the circulation subsequent to this period are to be explained principally by the withholding of fluids and food and the maintenance of the animals in the dorsal position on the table.[6] The presence of the two small wounds in the legs did not appear to be an important factor, even though there was some infection present. The remarkable feature about the circulation during this period was the persistence of the blood pressure at extremely low levels for long periods before circulatory failure and death came about.

In group 2, in which fluids and food were given postoperatively, the significant feature was the persistence of the blood pressure in the vicinity of critical levels during the initial period of spinal shock and for four to six days thereafter, without the development of surgical shock and with subsequent gradual recovery.

The strong resistance of the animals of both groups to the low blood pressures under conditions of the two types of experiments is best explained by the fact that with the arterioles and capillaries dilated and with but little loss of blood from operation, the tissues received a larger supply of blood and were better nourished than the level of blood pressure alone would indicate; consequently, surgical shock and death came relatively late in group 1 and were avoided in

6. Eversole, J. W.; Kleinberg, W.; Overman, R. R.; Remington, J. W., and Swingle, W. W.: Am. J. Physiol. **140**:490, 1944.

group 2. This explanation is supported by the work of Freeman and associates,[7] who found that the blood pressure could be reduced to a lower level for a longer period by bleeding without the production of fatal shock in a totally sympathectomized dog than in a normal dog. This was due to the better nutrition of tissues as a result of the vasodilation, the greater peripheral blood flow and the smaller amount of bleeding required to lower the blood pressure in the sympathectomized animal. It is also supported by the observation [3] that rabbits are remarkably resistant to shock from hemorrhage when the bleeding is carried out while the blood pressure is greatly lowered by inhibition of the vasoconstrictor nerves and vasodilation of arterioles and capillaries from stimulation of the aortic depressor nerves.

The hemodilution one hour after section of the cord in group 1 and three hours after section in group 2, as indicated by decreases in the red cell, hemoglobin and hematocrit determinations on blood from the femoral artery, appears to be best explained, in conjunction with the blood volume studies, by the trapping of red cells in the tissues. There appears to have been little absorption of fluids from the tissues by the blood, as might be expected from the reduction in hydrostatic pressure. This finding was confirmed by analyses of tissue. The terminal shift toward hemoconcentration in group 1 is not well understood, but it supports the theory of leakage of plasma as a result of capillary damage. The bloody fluid in the bowel appeared to be richer in plasma than in red cells, which would explain the greater terminal hemoconcentration in this group.

The persistence of the plasma volume in group 2 in the vicinity of normal during the first three to four and one half hours, with a definite reduction of the red cell mass, may be an indication of trapping of the red blood cells in the tissues with little or no influx of tissue fluids into the blood stream.

The most significant biochemical changes found in the blood of both groups of dogs were evidently results of functional disturbances. The sluggishly flowing blood within dilated capillaries disturbed the vital functions of the blood. The most significant disturbances noted were:

1. An anemic anoxia, which existed in all dogs. This anoxia caused a reduction in the volume of oxygen furnished to the tissues of the body and therefore evidenced incomplete oxidation. This impaired blood supply of oxygen may have depressed the circulation still more.

2. A fall in the carbon dioxide content of the serum, which denoted a depletion in the alkali reserve and further evidenced incomplete oxidation.

3. A decreased serum protein concentration, probably the result of many factors operating simultaneously.

The acute degenerative changes in certain of the viscera are results of deficient circulation. The loss of a bloody fluid into the lumen of the intestine, most noticeable in the jejunum and duodenum, occurred secondary to a breakdown of intestinal villi, due in part to the deficient circulation and in part to the digestive action of the intestinal jüices.

SUMMARY AND CONCLUSIONS

The state of pronounced general depression and low blood pressure known as spinal shock, which follows section of the eighth cervical segment of the spinal cord in dogs, does not lead to surgical shock if the animals are given adequate fluids, food and nursing care. The general depression gradually improves, while the blood pressure persists at the upper limits of the shock level for four to six days before the onset of a slow, gradual elevation to preoperative levels. During this acute period of vasodepression there is additional evidence of impairment of the circulation, as shown by a moderate to severe reduction in erythrocytes, hemoglobin and red cell volume. Limited studies indicate a slight reduction in total blood volume. There is also a significant reduction in the serum protein and the oxygen and carbon dioxide content of the blood. Changes in the water, chloride and sodium concentrations are small. Calcium concentrations are reduced, while potassium concentrations show a noticeable rise. The most important cause of these changes appears to be the trapping of erythrocytes in the tissues under conditions of vasodilation and low blood pressure.

When, after section of the cord, the animals were kept in the dorsal position on the operating table, with wounds in each thigh for the insertion of cannulas in the femoral arteries and with fluids and food withheld, they reacted the same as the other group of animals during the first six to twelve hours. Thereafter, the general depression began to increase and the blood pressure declined, usually to very low levels, where it remained for from twelve to twenty-four hours,

7. Freeman, N. E.; Shaffer, S. A.; Schecter, A. E., and Holling, H. E.: J. Clin. Investigation **17**:359, 1938.

with the animals in a state of shock until death occurred. The hematologic changes were similar to those of the earlier period of the first mentioned group except that there was a terminal trend toward hemoconcentration. Necropsy revealed evidence of acute degenerative changes in some of the tissues, which were interpreted as due primarily to anoxia.

In both types of experiments the animals were definitely more resistant to low blood pressure than has been found to be the case with animals in which the blood pressure has been reduced to equally low levels by hemorrhage or local loss of fluid from injury. This is interpreted as due to the fact that after the section of the cord there are vasodilatation and better nutrition of the tissues than is the case after straight hemorrhage or the local loss of fluid from injury with low blood pressure in which there is vasoconstriction.

The observations support the view that a low blood pressure produced by the exclusion of vasoconstrictor activity, whether from direct injury of pathways or from reflex inhibition, causes less impairment of the circulation and less tendency to shock than does an equally low blood pressure produced by hemorrhage or by local loss of fluid from injury.

The administration of adequate amounts of water, electrolytes and food protects against circulatory failure when the blood pressure is at a low level as a result of exclusion of vasoconstrictor activity by spinal cord injury.

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HEMODYNAMIC AND BIOCHEMICAL CHANGES IN DOGS SUBJECTED TO SECTION OF THE SPINAL CORD

CHANGES IN DOGS SURVIVING OPERATION FOR PROTRACTED PERIODS

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In a previous paper[1] studies were reported of the physiologic and biochemical changes that occurred in dogs during the acute stage of low blood pressure following section of the spinal cord at the eighth cervical segment in order to determine their bearing on the syndrome of surgical shock. In that study two groups of animals were used. One group was given adequate care following section so that recovery and survival within the limits of the surgical procedures performed might be reasonably assured. Inasmuch as there is little detail in the literature concerning shifts of electrolytes and other biochemical shifts that occur during the recovery of animals from the state of low blood pressure and "spinal shock" following section of the cord, it was believed that further studies on this surviving group would provide useful data. Also, it was thought that the information obtained from these biochemical studies might have some bearing on the management of patients with low blood pressure during the early period of injury high in the spinal cord.

In dogs in which high section of the cord is followed by adequate nursing care, the vasomotor paralysis caused by the interruption of nerve pathways running from the medulla to the cord centers results in a prolonged state of hypotension. For the first four to six days this remains fairly constant at pressure levels fluctuating between 60 and 80 mm. of mercury. After this acute period, the vasomotor centers in the cord below the site of section begin to assert their inherent power of autonomous action, and the lost vasoconstrictor tone is slowly but gradually reestablished. It was during this slow recovery phase that the following hemodynamic and biochemical studies were made.

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1. Phemister, D. B.; Eichelberger, L., and Laestar, C. H.: Early Effects on Dogs of Section of the Eighth Cervical Segment of the Spinal Cord and Their Bearing on Shock, Arch. Surg., this issue, p. 32.

EXPERIMENTAL PROCEDURES AND METHODS

Five dogs, 4 females and 1 male, (under evipal sodium anesthesia [40 mg. per kilogram of body weight]) were operated on aseptically and the spinal cord sectioned at the eighth cervical segment. Blood loss was very small (under 50 cc.) except in 1 animal, in which the blood loss was replaced by a blood transfusion. Postoperatively, the animals were given intravenous injections of 10 per cent dextrose in Ringer's solution for several days. They received milk and eggs, which were given at first by gavage and after a short time taken voluntarily. This diet was continued at a maintenance level throughout the experiments. Urine was expressed by suprapubic compression for the first two weeks following section.

Dogs 294 and 302 were observed for blood pressure changes only, while dogs 234, 237 and 238 were studied for blood pressure and biochemical changes. Blood pressure readings and samples of blood were obtained by puncture of an unexposed femoral artery, and replacement transfusions given as described in the previous paper. Blood was taken daily during the first week, on alternate days during the second week and then at progressively longer intervals until the time of killing. The chemical methods and procedures used were those employed in previous studies by one of us.[2] The analytic data were subjected to the same kind of calculations as those employed in the former study[1] to estimate the changes in the serum and the cells in per cent of the control values.

Dog 234 was observed for one hundred and nineteen days before it was killed, at which time the blood pressure had returned to the vicinity of preoperative levels. Dogs 302, 294 and 237 were sacrificed at the end of seventy-seven days, seventy-four days and thirty-nine days, respectively, for other experimental purposes. Dog 238 met death accidentally on the thirteenth day following section. Although this paper is concerned only with the chronic phase of these experiments, all tables and figures show complete data from the time of section of the cord to the death of the animal so that comparisons with the acute phase can be made.

RESULTS

By the fourth to the sixth day following section of the cord the general condition of the animals had started to improve, and within two

2. (*a*) Eichelberger, L., and Roma, M.: J. Urol. **40**: 366, 1938. (*b*) Eichelberger, L.: J. Biol. Chem. **128**: 137, 1939. (*c*) Eichelberger, L., and Bibler, W. O.: ibid. **132**:645, 1940.

weeks the spinal wounds were healed and the pulse, respirations and temperatures had returned to normal ranges. The postoperative course was uneventful up to the time of termination of the experiments, except for a mild cystitis in dog 238, which was healing at the time of death. Occasional small pressure sores appeared on the hips, but they healed rapidly under proper care and never became an influential factor on the general condition of these animals.

Incontinence of stools was established soon after operation, and by the fourth to the sixth day the bladder had started to empty involuntarily. There was no gross evidence of blood in the stools of any of the animals. Flexor and knee jerk reflexes had been regained almost immediately after section of the cord in all experiments, but flaccid paralysis of the hindquarters was complete. In dog 234 slight extensor tone became manifest toward the latter part of the second month, and by the time of killing, one hundred and nineteen days after section, it had become sufficiently strong to support momentarily the weight of the animal when placed on its feet. Throughout the course of the experiments, the body weights, with but 1 exception, remained constant or showed a slight increase (table 1).

TABLE 1.—*Body Weights in Kilograms of Five Dogs Taken at Varying Intervals Following Experimental Section of the Spinal Cord at the Eighth Cervical Segment*

Days After Section	Dog 234	Dog 294	Dog 302	Dog 237	Dog 238
0	8.9	13.0	15.0	14.0	11.4
7	8.9	12.1			
10-15	9.0	12.8	15.8	....	11.6
22-24	9.2	12.8	16.4	12.7	
33-39	8.9	13.9	16.3	11.8	
41-43	8.8	14.2	16.1		
59-64	8.4	14.1	17.3		
69-72	8.9	14.3	16.9		
74-77	...	14.7	17.0		
87	8.9				
119	8.8				
	Killed 119th day	Killed 74th day	Killed 77th day	Killed 39th day	Killed 13th day

Disuse atrophy in the hindquarters became apparent after the first month, however, and by the time that dog 234 was killed the muscles were greatly wasted, and necropsy revealed the cortex of the femurs to be extremely thinned. Function of the forelegs was not intensely disturbed in any of the animals and became sufficiently strong within a week or two to support body weight and assist in movement.

Blood Pressure.—Chart 1 shows a composite curve of the blood pressure levels of 5 dogs for the first ten days, 4 dogs for the next twenty-nine days and 3 dogs for the next four days after section of the cord. Table 2 shows blood pressure levels for the entire survival period of each animal of the group. These readings were recorded at the same time samples of blood were withdrawn. Although the blood pressure started rising by the end of the first week, the

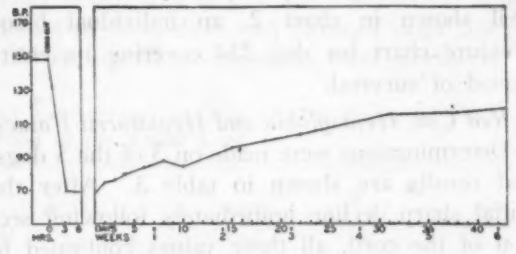

Chart. 1.—Composite curve of blood pressures.

TABLE 2.—*Mean Blood Pressures of Five Dogs Following Experimental Section of the Spinal Cord at the Eighth Cervical Segment*

Days After Section	Dog 234, Mm. Hg	Dog 302, Mm. Hg	Dog 294, Mm. Hg	Dog 237, Mm. Hg	Dog 238, Mm. Hg
Control.....	140	158	146	130	170
0.13.....	70	60	80	80	58
1.....	80	68	60	68	60
2.....	70	68	90	80	64
3.....	72	92	70	68	80
4.....	73	82	80	80	80
6.....	80	82	86	80	78
8.....	90	84	90	100	70
10.....	70	88	96	86	78
15.....	85	100	110	84	Killed 13th day
22.....	100	100	112	98	
29.....	...	108	120		
31.....	110	...	...	120	
38.....	...	...	122	116	
39.....	...	...	...	110	
42.....	115	...	...	Killed	
43.....	...	120	120		
56.....	...	120	138		
59.....	108				
71.....	...	120			
72.....	125				
73.....	...	...	125		
74.....	...	...	115		
77.....	...	125	Killed		
87.....	120	Killed			
119.....	150				
	Killed				

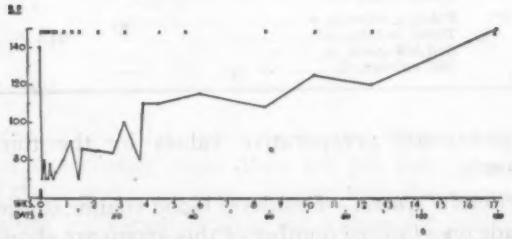

Chart 2. (dog 234).—Blood pressure curve during period of recovery.

levels obtained were unstable for three to four weeks. This phase ended, and from that time on the progress was smooth and gradual to increasingly higher pressure levels. This is well shown in chart 2, an individual blood pressure chart for dog 234 covering its entire period of survival.

Red Cell, Hemoglobin and Hematocrit Values.—Determinations were made on 3 of the 5 dogs, and results are shown in table 3. After the initial sharp decline immediately following section of the cord, all three values continued to decline or fluctuated around previously low levels for ten days in dog 234, during the first ten days of the thirteen day survival period of dog 238 and for two weeks in dog 237. After this they rose slowly until in dog 234 they reached the approximate preoperative values by the third month.

Blood Volume.—Results of blood volume studies made on a limited number of this group are shown in table 4. It will be noted that the total blood volumes on the twenty-second day for dogs 234 and 237 were lower than the control volumes and approximately the same as those taken seventy-five hours after section. At the same time, the plasma volumes had increased and the red cell mass had severely decreased.

Electrolyte, Protein and Water Content of Serum and Cells of Normal Dogs over a Period Preceding the Experimental Section of the Cord.—To estimate the extent of variation in blood constituents in any 1 normal animal over a period previous to experimental procedures, 2 animals were isolated in metabolism cages for four months before the start of the experiments and blood analyses were carried out during the first month.

The data obtained from the analyses of serum and whole blood of dogs 237 and 238 are given in table 5. The contents of the cells were calculated indirectly from the values for whole blood and serum and the cell volume. It was important to determine the range of individual variation over a period of time, so that real differ-

TABLE 3.—*Cell Count, Cell Volume and Hemoglobin Determinations on Three Dogs Following Experimental Section of the Spinal Cord at the Eighth Cervical Segment*

Time After Section, Days	Dog 234			Dog 237			Dog 238		
	R. B. C., M.	Hb., Gm.	Cell Vol., %	R. B. C., M.	Hb., Gm.	Cell Vol., %	R. B. C., M.	Hb., Gm.	Cell Vol., %
Control	9.02	18.1	53.5	7.32	18.0	51.0	5.70	13.6	36.5
0.13	7.30	14.1	43.0	6.26	15.1	41.0	4.40	10.1	31.0
1	5.78	12.2	37.0	5.54	12.5	36.5	4.06	9.4	27.0
2	5.20	10.7	33.0	4.84	11.2	34.5	4.18	9.6	26.5
3	4.94	10.3	32.0	4.64	10.2	29.5	4.22	9.8	28.0
4	4.67	9.8	28.5	5.10	12.3	31.5	3.50	8.3	25.0
6	4.40	9.4	26.5	4.70	10.8	33.5	3.54	8.5	25.5
8	4.78	9.7	30.0	4.02	9.3	29.5	4.08	9.4	27.0
10	5.00	10.2	30.0	4.08	9.2	29.0	3.66	8.4	28.0
15	5.73	11.3	34.0	3.78	8.7	28.0		Killed 13th day	
22	5.92	11.8	37.5	4.68	10.2	33.0			
31	7.44	14.6	47.5	5.70	12.9	42.0			
38	7.72	15.6	49.5	5.84	13.2	41.5			
59	8.68	17.9	56.0		Killed 39th day				
72	8.64	17.2	56.0						
87	8.66	17.6	59.5						
119	9.40	18.8	56.1						
		Killed 119th day							

TABLE 4.—*Blood Volumes by Evans Blue Dye Method on Dogs Surviving Experimental Section of the Spinal Cord at the Eighth Cervical Segment*

Dog	Determination	Controls		After Cord Section			
		Weight, Kg.	24 Hr. Before Section	3.0 to 4.5 Hr.	75 Hr.	Weight, Kg.	22d Day
234	Plasma volume, cc.		360	395	530		490
	Total volume, cc.	8.9	855	675	730	9.2	780
	Red cell mass, cc.		495	280	200		290
	Cell volume, %		57.5	42.0	270		37.0
237	Plasma volume, cc.		655	668	816		767
	Total volume, cc.	14.0	1,393	1,103	1,150	12.7	1,112
	Red cell mass, cc.		738	435	334		345
	Cell volume, %		53.0	39.5	29.0		31.0
238	Plasma volume, cc.		600	632	518		
	Total volume, cc.	11.4	1,092	902	720		
	Red cell mass, cc.		492	270	202		
	Cell volume, %		45.0		28.0		

ences in the samples from the same animal after experimental procedures could be better estimated.

Electrolyte, Protein and Water Content of Serum and Cells Following the Experimental Section of the Spinal Cord.—The experimental

Serum.—It will be observed that the total serum protein decreased sharply over a period of four days following the cutting of the cord, after which that of dog 238 returned to normal limits in eight days and those of dogs 234 and 237 required approximately three weeks for the

TABLE 5.—*Concentration of Constituents of Serum and Erythrocytes in Dogs Over a Period of Time Preceding Experimental Section of the Spinal Cord*

(Values are expressed in units per liter)

	Sample Date	H_2O, Gm.	Cl, mM	Na, mM	K, mM	Total Protein, Gm.	Cell * Volume, %	O_2 † Content, mM
Dog 237								
				Serum				
	6/21	928.4	110.3	141.0	4.67	61.9		
	6/28	936.2	110.7	138.5	4.36	58.1		
	7/21	937.0	118.7	137.1	4.63	57.1		
	10/12	939.3	114.4	142.7	4.57	54.8		
	Average	935.3	113.5	139.8	4.56	58.0		
	‡	3.6	3.4	2.2	0.12	2.6		
				Erythrocytes				
	6/21	712	61.1	95.5	8.59	....	57.3	10.10
	6/28	713	77.2	85.3	8.25	....	50.4	8.72
	7/21	698	59.7	98.8	9.76	....	48.6	8.78
	10/12	711	55.8	86.5	11.28	....	50.9	9.40
	Average	708	63.4	91.3	9.47	....	51.8	9.25
	‡	2	8.2	7.3	1.18	....	3.3	5.53
Dog 238								
				Serum				
	6/23	930.7	115.2	142.5	4.57	60.7		
	6/30	936.4	113.8	145.1	4.20	61.8		
	7/21	937.0	119.4	143.7	4.20	57.0		
	10/26	931.9	115.5	141.8	3.83	57.2		
	Average	934.0	116.0	143.3	4.20	59.2		
	‡	2.7	3.5	1.2	0.26	2.1		
				Erythrocytes				
	6/23	706	63.3	102.2	7.70	....	47.8	9.17
	6/30	712	64.2	92.7	11.18	....	46.6	8.39
	7/21	713	66.2	82.3	9.08	....	44.6	9.25
	10/26	696	58.0	100.3	11.96	....	36.6	7.66
	Average	707	62.9	94.4	9.98	....	43.9	8.62
	‡	7	3.0	7.8	2.06	....	1.9	0.65

* Cubic centimeters per hundred cubic centimeters of blood.
† Millimols per liter of whole blood.
‡ Standard deviation

TABLE 6.—*Changes in Red Cell Volume and Oxygen Content (in per Cent of the Control Values) of Whole Blood from Dogs Surviving Experimental Section of the Spinal Cord at the Eighth Cervical Segment*

Sample	Time After Section, Days	Dog 234		Dog 237		Dog 238	
		Cell Volume, %	O_2 Content, mM/L	Cell Volume, %	O_2 Content, mM/L	Cell Volume, %	O_2 Content, mM/L
Control	0	53.7	10.24	50.9	9.40	36.6	7.66
		Δ%	Δ%	Δ%	Δ%	Δ%	Δ%
2	0.13	−19.5	−19.1	−19.4	−14.05	−15.8	−20.22
3	1	−30.7	−36.5	−28.3	−21.28	−26.2	−12.54
4	2	−38.8	−36.7	−32.4	−28.70	−27.6	−10.44
5	3	−40.6	−26.1	−41.6	−41.20	−23.8	−31.70
6	4	−47.0	−43.1	−37.9	−35.30	−31.1	−36.40
7	6	−50.3	−52.0	−34.0	−33.90	−30.6	−34.70
8	8	−44.5	−37.5	−42.0	−42.90	−25.9	−34.45
9	10	−44.0	−33.2	−43.4	−40.00	−24.0	−36.95
10	15	−36.4	−37.6	−44.8	−45.10		
11	22	−29.8	−32.3	−35.0	−39.15		
12	31	−11.9	−17.5	−17.7	−19.25		
13	38	− 7.4	−13.6	−18.4	−22.32		
14	50	+ 4.3	− 4.5				
15	72	+ 3.9	− 2.8				
16	87	+10.4	+ 0.3				
17	119	+ 4.3	± 0				

and calculated data for the serum and cells of dogs 234, 237 and 238 are given in tables 6, 7, 8 and 9. By a comparison of the experimental values with the control values, the changes have been expressed in per cent of the original concentration (ΔH_2O, ΔCl, etc.).

return. At the same time, the serum water did not change more than 1.8 per cent in any of the dogs at any time. Along with the lowered values for serum protein the values for calcium were decreased in dogs 234 and 237. Fluctuations in the concentration of total calcium oc-

TABLE 7.—*Changes in Water, Electrolytes and Protein Concentrations (in per Cent of Control Values) in the Serum and Erythrocytes Following Experimental Section of the Spinal Cord at the Eighth Cervical Segment*

Dog 234

(Values are expressed in units per liter)

Serum

Sample	Time After Section, Days	Total CO_2, mM	H_2O, Gm.	Cl, mM	Na, mM	K, mM	Ca, mM	Mg, mM	Total Protein, Gm.
Control	0	24.40	932.0	104.3	141.2	4.14	3.02	1.02	61.4
		Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %
2	0.13	— 4.87	+0.53	+ 2.06	— 3.47	+ 5.07	.....	.....	— 8.30
3	1	—19.44	+1.82	+ 1.87	— 5.95	— 7.73	—18.55	+ 4.90	— 4.73
4	2	—14.44	+1.18	+ 2.25	— 4.04	+ 3.62	—19.88	+18.62	—12.38
5	3	—18.15	+1.39	+ 4.18	— 3.33	+14.00	—20.88	— 0.98	—17.10
6	4	—13.20	+1.18	+ 2.06	— 3.40	+ 2.66	—26.50	+ 6.86	—26.55
7	6	—18.65	+1.07	+ 5.16	— 6.66	+16.45	—18.55	+ 3.92	—16.78
8	8	— 8.60	+0.40	+ 6.10	— 5.24	+34.80	—16.65	+11.76	— 4.56
9	10	—12.71	±0	+ 6.48	— 3.62	+37.20	— 9.96	— 5.88	— 8.96
10	15	— 8.40	+0.53	+ 7.96	— 2.76	+34.80	—15.90	—15.70	— 8.14
11	22	—10.16	+0.53	+ 5.64	+ 3.40	+38.90	—18.20	+ 4.9	—10.91
12	31	— 3.52	±0	+ 5.17	— 2.06	+32.40	—18.20	—15.70	± 0
13	38	—15.78	+0.75	+ 8.18	— 3.68	+33.82	— 5.96	— 7.84	— 5.22
14	59	.....	+0.21	+ 6.67	— 3.83	+30.90	.....	.....	— 3.26
15	72	—26.00	±0	+ 8.26	— 4.61	—34.80	— 0.66	+14.70	— 3.26
16	87	—28.10	—0.40	+ 7.52	+ 1.63	+30.90	.....	.....	— 0.65
17	119	—21.92	±0	+ 6.20	— 2.62	+19.60	.....	.....	+ 0.49

Erythrocytes

			Gm.	mM	mM	mM
Control	0	.....	708.0	54.0	98.0	5.83
			Δ %	Δ %	Δ %	Δ %
2	0.13	.....	+1.28	— 0.18	+ 6.12	+19.05
3	1	.....	+5.41	+ 2.04	— 5.10	+66.0
4	2	.....	—4.98	— 7.04	—10.63	+62.8
5	3	.....	+3.12	—10.20	+ 2.04	+61.6
6	4	.....	±0	—12.95	— 4.80	+66.0
7	6	.....	+2.13	— 8.34	+20.00	+74.4
8	8	.....	—0.42	+ 8.89	—22.95	+143.5
9	10	.....	+3.85	+17.78	—14.08	+165.8
10	15	.....	+2.85	+ 2.41	+ 0.33	+ 87.3
11	22	.....	—1.14	+14.80	+ 5.51	+136.0
12	31	.....	+3.85	+36.6	+ 5.00	+127.0
13	38	.....	+3.27	+11.85	+ 8.78	+118.0
14	59	.....	+1.56	+17.08	+ 7.34	+33.1
15	72	.....	+2.13	+19.43	+ 7.04	+61.6
16	87	.....	+3.85	+37.2	+ 2.24	+51.6
17	119	.....	+0.85	+62.9	— 5.20	+ 4.98

TABLE 8.—*Changes in Water, Electrolytes and Protein Concentrations (in per Cent of Control Values) in the Serum and Erythrocytes Following Experimental Section of the Spinal Cord at the Eighth Cervical Segment*

Dog 237

(Values are expressed in units per liter)

Serum

Sample	Time After Section, Days	p_H	Total CO_2, mM	H_2O, Gm.	Cl, mM	Na, mM	K, mM	Ca, mM	Mg, mM	Total Protein, Gm.
Control	0	7.47	20.30	939.8	114.4	142.7	4.57	2.44	0.89	54.8
		±	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %
2	0.13	—0.05	— 6.65	+0.98	+ 4.64	— 0.63	—16.2	— 4.10	+11.25	— 3.3
3	1	+0.08	—28.4	+0.53	— 0.18	— 1.54	— 3.28	— 7.38	+23.05	— 7.3
4	2	+0.01	— 6.50	+1.32	+ 0.35	— 3.78	+12.05	—15.58	± 0	—20.2
5	3	+0.03	— 2.96	+0.41	+ 1.58	— 1.89	+11.80	—16.40	—29.20	—12.9
6	4	—0.04	+ 4.63	+0.85	— 4.46	— 4.91	+17.73	—14.75	—29.20	—16.0
7	6	+0.05	— 6.55	+0.67	— 0.18	— 2.38	+ 2.41	— 7.38	—29.20	—12.0
8	8	+0.05	— 0.94	+0.65	— 3.50	— 5.75	+25.60	— 5.73	+14.60	—10.0
9	10	+0.03	— 1.38	+0.56	— 2.89	— 2.59	+18.80	—18.45	+ 2.25	— 8.7
10	15	+0.05	— 4.93	+0.23	+ 5.77	— 2.59	+11.80	— 9.74	+ 5.62	— 3.10
11	22	±0	+ 1.61	+0.38	— 1.49	— 3.80	+23.40	— 3.69	+13.48	— 1.4
12	31	—0.05	+ 0.69	—0.18	— 4.02	— 4.07	+28.70	— 3.69	— 5.62	— 0.7
13	38	—0.04	— 0.79	—0.03	+ 0.44	— 0.70	+15.10	— 0.82	+12.35	+ 7.5

Erythrocytes

				Gm.	mM	mM	mM
Control	0	.....	.....	822.7	85.6	114.0	7.98
					Δ %	Δ %	Δ %
2	0.13	.....	.....	+2.53	— 4.09	+ 6.18	— 2.63
3	1	.....	.....	+4.59	+ 9.11	+ 6.05	— 8.56
4	2	.....	.....	+4.46	+ 9.11	+ 5.19	—15.90
5	3	.....	.....	+6.73	+13.06	+ 9.88	— 6.64
6	4	.....	.....	+5.43	+ 5.36	+ 2.64	— 1.25
7	6	.....	.....	+5.68	+10.74	+ 3.95	— 7.52
8	8	.....	.....	+5.28	+15.54	+ 7.16	—16.03
9	10	.....	.....	+6.34	+14.25	+ 3.38	—17.28
10	15	.....	.....	+6.48	+12.50	+ 4.78	—10.53
11	22	.....	.....	+5.81	+12.38	+ 4.37	—21.30
12	31	.....	.....	+2.94	+ 3.04	+ 2.22	—13.28
13	38	.....	.....	+3.21	+ 8.18	+ 7.50	—20.05

curring secondarily in response to fluctuations in the concentration of total protein are necessary for the maintenance of normal calcium ion concentrations.[3] The values for serum potassium reached their highest levels after the sixth day following the operation and remained high until the dogs were killed.

Cells.—The following changes in the cell values were found to accompany the protein and electrolyte disturbances recorded in the serum: namely, an increased cell water content throughout the period; a distinct increase in potassium content in dog 234 throughout a period of eighty-seven days, with the highest values occurring from the eighth to thirty-eighth day after operation, while in dog 237 the opposite, a decrease in the potassium content, was found, and a significant fall in the cell volume accompanied with a decreased oxygen content, the greatest and most constant decline occurring from the fourth to the fifteenth day following the cutting of the cord.

Observations at Necropsy.—In all animals the spinal cord was found to have been cleanly severed at the eighth cervical segment, and the cut ends were separated by fibrous tissue growth. A recent impaction in the lower bowel and thickening of the urinary bladder in dog 234 were the only gross evidences of visceral pathologic change found in any animal. No sections of tissue were taken for microscopic examination.

COMMENT

To summarize the data for the 3 dogs, mean average concentrations were estimated for all constituents for the initial blood sample and for all experimental samples thereafter. The mean changes in per cent of the average initial concentration were plotted and are shown in chart 3 for serum and chart 4 for cells.

The period represented for four days on the curves is roughly the period of "spinal shock," which has been discussed in the preceding paper. The days that follow are considered as the recovery period. Despite a relative constancy of serum water, the serum proteins increased from an average low value of 4.8 Gm. per hundred cubic centimeters on the fourth day to 5.4 Gm. per hundred cubic centimeters on the eighth day after operation. For fourteen days more the serum proteins remained at this low level, after which they returned gradually to normal. This fact indicates slight hemodilution, which may have been in part a result of the entrance of interstitial fluid into the blood stream from elsewhere in the body. This is evidenced by the slight gains in the serum water (0.5 to 1 per cent) and chloride (2 to 4 per cent) and the decreases in sodium (3 to 5 per cent). Fur-

TABLE 9.—*Changes in Water, Electrolytes and Protein Concentrations (in per Cent of Control Values) in the Serum and Erythrocytes Following Experimental Section of the Spinal Cord at the Eighth Cervical Segment*

(Values are expressed in units per liter)

Sample	Time After Section, Days	p_H	Total CO_2, mM	H_2O, Gm.	Cl, mM	Na, mM	K, mM	Ca, mM	Mg, mM	Total Protein, Gm.
Dog 238										
Serum										
Control	0	7.38	17.55	931.9	115.5	141.8	3.83	2.25	1.07	57.2
		±	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %	Δ %
2	0.13	+0.04	—14.15	+1.40	+ 3.29	+ 1.39	— 7.04	+ 9.78	+18.7	—11.90
3	1	+0.07	—10.76	+1.35	— 3.03	+ 4.52	± 0	+ 6.22	+ 5.61	—12.40
4	2	±0	—13.40	+1.80	+ 5.64	+ 3.97	+ 5.48	— 5.34	+ 3.74	—22.90
5	3	±0	—20.10	+1.64	+ 2.60	— 4.31	+19.60	—11.10	+19.6	—23.09
6	4	+0.11	+15.90	+1.72	— 3.64	— 2.71	+13.85	+10.21	.....	—20.10
7	6	+0.07	+12.95	+1.01	— 3.21	— 1.60	+23.75	+ 7.56	+32.70	—10.50
8	8	+0.05	+13.05	+0.97	— 0.26	+ 4.87	+56.90	+10.21	+10.28	— 0.87
9	10	±0	+ 4.13	+0.90	+ 3.28	— 1.46	+30.55	+ 4.44	+15.90	— 7.86
Erythrocytes										
				Gm.	mM	mM	mM			
Control	0	.....	.....	696.0	58.0	100.3	11.96			
				Δ %	Δ %	Δ %	Δ %			
2	0.13	.....	.....	+1.82	+ 5.68	+ 0.40	+23.75			
3	1	.....	.....	+1.41	+64.6	+ 2.89	+21.00			
4	2	.....	.....	+0.14	+ 9.30	—13.05	+22.65			
5	3	.....	.....	+2.82	+13.10	—12.45	+23.10			
6	4	.....	.....	+3.24	+ 9.48	+25.80	—12.38			
7	6	.....	.....	+3.24	+ 1.35	+ 6.68	— 6.52			
8	8	.....	.....	+0.71	+ 9.48	+ 3.58	— 0.33			
9	10	.....	.....	+3.95	+ 9.83	+17.45	—10.05			

3. McLean, F. C., and Hastings, A. B.: Am. J. M. Sc. 189:601, 1935.

thermore, the plasma volumes determined on the twenty-second day after operation for dogs 234 and 237 showed increases from control values of 360, and 655 cc., preceding the cutting of the cord, to 490 and 767 cc., respectively.

Although there was general improvement in the condition of the animals, the potassium in the serum was found to persist at high levels throughout the recovery period. In seeking the source of the potassium, the data show that

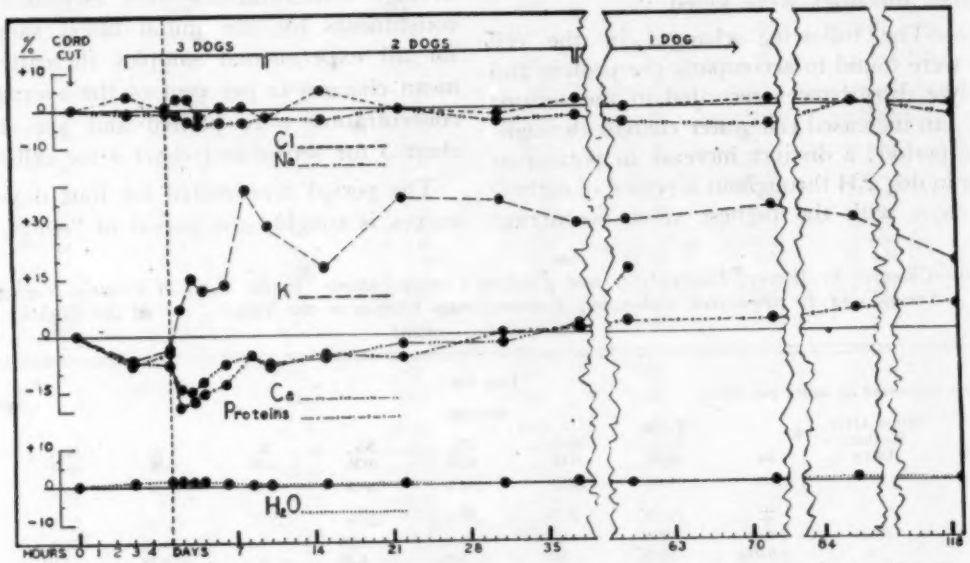

Chart 3.—Changes in serum. Mean changes in per cent of the average initial concentrations of chloride sodium, potassium, calcium, protein and water in serum

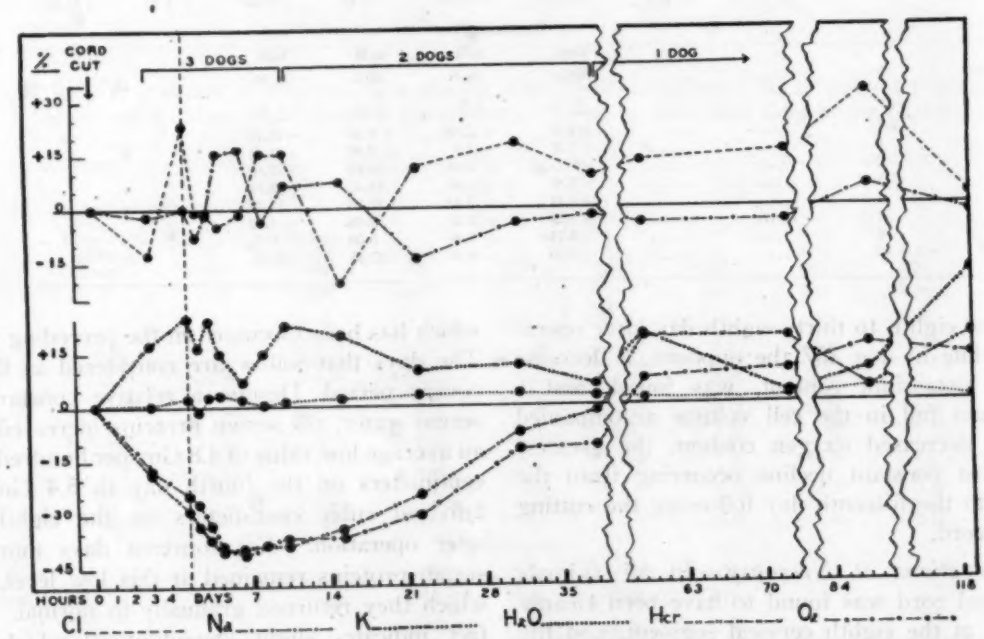

Chart. 4.—Changes in erythrocytes. Mean changes in per cent of the average initial concentrations of chloride, sodium, potassium and water in the erythrocytes and the cell volume and oxygen content of the blood.

In the conditions reported here, therefore, there is evidence of hemodilution during the recovery period but not sufficient to account for the lowered cell volume and cell count.

in dog 234 there were large increases in potassium in both the serum and the cells, which seemed to be the result of a liberation of and a shift from the intracellular to the extracellular

compartments and the blood stream. The liberation of potassium from the intracellular compartments may be a result of the anoxia of the tissues, including the vessel walls, for it is to be noted that the serum potassium persisted at an increased level as long as the cell volume and oxygen contents of the blood were low. Besides the low supply of oxygen at these low blood pressure levels, the blood flowed slowly through all capillaries below the level of section of the cord, thereby further reducing the rates of supply of the oxygen.

Manery and Solandt [4] have previously shown that animals with transected spinal cords exhibited an increase in the potassium in the blood from the jugular vein. In dog 237 the potassium shifted from the blood cells into the serum. It is well known that the chemical pattern of red cells may undergo wide changes in coming into equilibrium with the serum. In this connection, it will be observed that the blood cells gained water about to the extent of the serum sodium deficit.

The average cell volume (hematocrit) and oxygen content were lowest from the fourth to the eighth day following the operation and remained at very low and constant values for approximately twenty-one days (fig. 4). Although the blood pressures had risen to about 95 mm. of mercury on the fifteenth day, the cell volume and oxygen content of the blood were still 35 per cent lower than normal values. The explanation for these low values is problematic. Blood loss from operation was slight except in 1 case, in which it was compensated for by blood transfusion. Undernourishment, trapping and increased destruction of red cells and decreased hemopoiesis under conditions of low blood pressure call for consideration. That undernourishment was not the largest factor is suggested by the small loss of weight (table 1). While it is evident that during the earlier period of low blood pressure and loss of vasomotor tone many of the capillaries and especially the blood reservoirs had trapped numbers of red cells, this condition should have been alleviated gradually as the pressure rose; therefore it should not have been responsible for the low cell volume and oxygen content continuing for approximately three weeks after section. Other factors may have been operative to produce this, such as a retardation of hemopoiesis, an increased rate of destruction of red cells, an inability of the blood reservoirs (spleen, liver, etc.) to throw their reserve red cells into the circulation or a combination of any or all of these factors working simultaneously. Under conditions of reduced arterial oxygen content an acceleration rather than a retardation of hemopoieic activity of red bone marrow would be expected, as indicated by the many studies on the effect of anoxia on the blood.[5] Because of the numerous replacement transfusions, the possibility of hemolysis from incompatible bloods must be considered. The relative infrequency of transfusion reactions generally experienced speaks strongly against this explanation. Since determinative tests for blood pigments were not carried out, it cannot be said definitely what mechanisms were involved. This subject requires further investigation.

With the presence of a low blood pressure, peripheral vasodilatation in the paralytic region, a pronounced anemic anoxia and a blood stream flowing slowly for as long as thirty days, the volume of oxygen furnished to the tissues and cells of the body, as well as the rates of supply, is greatly reduced and the metabolic processes of all cells may therefore be disturbed and delayed.

SUMMARY

Five dogs surviving the circulatory embarrassment resulting from section of the spinal cord at the eighth cervical segment were studied for varying lengths of the recovery period to determine changes in blood pressure, hemoglobin and red cell count and volume and for biochemical changes in the serum and erythrocytes. Blood loss was very slight except in 1 case, in which a replacement transfusion was given. The various observations may be summarized as follows:

1. *Blood Pressure.*—The blood pressure fell promptly after section of the cord to values of 60 to 80 mm. of mercury, where it persisted for four to six days without resulting in circulatory failure. It then rose slowly to 90 to 100 mm. of mercury during the following two weeks and to the vicinity of 120 mm. of mercury in six weeks. In dog 234 the pressure returned to the preoperative level by the seventeenth week.

2. *Blood Changes.*—The blood of 3 dogs during the recovery period, as designated from the fourth postoperative day until the mean blood pressures returned in the main or completely to preoperative levels, was characterized by (1) a slight hemodilution, as evidenced by lowered serum proteins, little alteration in the serum chloride, water and sodium and increased plasma

4. Manery, J. F., and Solandt, D. Y.: Am. J. Physiol. **138**:499, 1943.

5. Van Liere, E. J.: Anoxia: Its Effect on the Body, Chicago, University of Chicago Press, 1942, p. 33.

volumes; (2) significant increases in the potassium of the serum as long as the oxygen content of the bloods was low, and (3) pronounced decreases in the cell volume (hematocrit), cell count and oxygen content of the blood for three to four weeks following operation.

The improvement in the anemia and the anoxia occurred simultaneously with the elevation of blood pressure.

The cause of the pronounced reduction in red cell count and volume (hematocrit) and oxygen content of the blood under conditions of paralysis from section of the cord at the eighth cervical segment and prolonged lowering of the blood pressure is not well understood. It is to be sought for (1) in trapping of red blood cells in the capillaries and blood reservoirs; (2) in an increase in plasma volume; (3) in an increased rate of red cell destruction from an undetermined cause; (4) in undernourishment, and (5) possibly in a retardation of hemopoiesis by the low blood pressure despite the presence of an anemic anoxia. Further studies are indicated for a more exact interpretation of the results.

Comparable findings in clinical cases of injury high in the spinal cord would call for appropriate medicinal therapy and blood transfusions for rehabilitation of the blood.

FRAGMENTATION AND DISSOLUTION OF GALLSTONES BY CHLOROFORM

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On certain occasions considerable difficulties arise during attempts to remove gallstones from the biliary tract. Calculi in the hepatic ducts found at the operation may tax the skill of a man with a wide experience in this type of work, not to speak of a general surgeon who encounters such conditions only once in a great while. W. Walters,[1] of the Mayo Clinic, cited a case in which he was not able to explore the intrahepatic duct on account of a large, anomalous hepatic artery crossing the duct. Obesity of the patient may also interfere with exploration of the hepatic ducts. Inflammatory processes, edema and adhesions may further complicate the situation.

Some stones lodged in the common duct require a transduodenal approach or an extensive mobilization of the duodenum for exposure of the retroduodenal portion of the ductus choledochus. Both technical procedures, even in the hands of the more experienced surgeon, considerably increase the operative risk because of the danger of infection and hemorrhage, especially great in the presence of cholemia.

It is not surprising that because of such technical difficulties repeated attempts have been made to develop effective substitute procedures, with special attention to the problem of dissolution or fragmentation of gallstones by chemical means.

According to Naunyn's[2] classification, gallstones can be divided into four groups: (1) pure cholesterol stones; (2) pure pigment-calcium, or "mulberry," stones (the pigment may be either bilirubin or biliverdin); (3) mixed calculi consisting mainly of cholesterol, calcium bilirubinate and calcium carbonate, and (4) pure calcium carbonate stones. The last group can be disregarded for the purposes of this study because stones of this type are found mostly in animals and rarely in man.

Inasmuch as in many instances the character of the stone cannot be determined in the course of the operation, a desirable solvent would be one which acts on both cholesterol and pigment. Calcium and also the binding mucoid substances which serve as the organic framework for the precipitated elements of the bile are reduced to a soft pulp which can be easily washed out by bile flow after a fragmentation of the stones has been accomplished.

Obviously the substance employed for this purpose must meet two requirements: It must have a strong solvent action on the stones, and it must be innocuous for the living tissues.

Attempts to find a suitable substance have been made repeatedly. In 1901 Walker[3] cited a case in which he used an ether-glycerin mixture to dissolve a stone by irrigation through a biliary fistula. Wright[4] reported a case in which a stone impacted in the common duct could be removed only after injection of turpentine. Pribram[5] recommended daily injections of ether through a T tube in cases in which a stone is firmly lodged in the papilla or in which the least suspicion exists that all the concrements have not been removed. He noticed that unless the tube is left open after the injection has been completed epigastric distress results from the vaporization of the ether, which takes place at body temperature. Walters and Wesson[1] obtained a fragmentation of a stone with injections of ethyl ether on three successive days and two subsequent injections of a solution consisting of one-third ethyl alcohol and two-thirds ethyl ether, as suggested by Osterberg. However, nausea and severe pain in the right upper quadrant of

Dr. Warren H. Cole made valuable suggestions in the preparation of this paper and granted us the privilege of performing the experiments in the laboratory of the department of surgery, University of Illinois College of Medicine.

1. Walters, W., and Wesson, H. R.: Fragmentation and Expulsion of a Common Duct Stone into the Duodenum Using Ether and Amyl Nitrite: Preliminary Report, Proc. Staff Meet., Mayo Clin. **12**:260, 1937.

2. Naunyn, cited by Darling, H. C.: Cholelithiasis (Latent and Active), M. J. Australia **2**:555, 1941.

3. Walker, cited by Raffl, A. B.: Experimental Studies on the Solvent Action of Ether on Gallstones, Am. J. Surg. **52**:65, 1941.

4. Wright, G.: The Value of Turpentine in Gallstone Operations, Brit. M. J. **2**:1808, 1908.

5. Pribram, B. C.: Zur Beseitigung eingeklemmter Choledochuspapillensteine, Deutsche med. Wchnschr. **58**: 1167, 1932; New Methods in Gallstone Surgery, Surg., Gynec. & Obst. **60**:55, 1935.

the abdomen following the last injection required an inhalation of amyl nitrite. A mixture of one-third ethyl alcohol and two-thirds ethyl ether in amounts of 5 cc. injected daily into the T tube for five or six days respectively was used with success in 2 cases by Morton.[6] Hunt [7] reported good results from injections of ether in patients with impacted gallstones. Burgess [8] observed pain after injections of ether in a patient and attributed it to the pressure generated by evaporation of the solvent at body temperature.

Probstein and Eckert [9] approached the problem experimentally and found that ether may be extremely toxic to dogs when injected directly into the biliary tract. Once the injections began, all the dogs became listless, had poor appetite, appeared extremely weak and lost weight. The authors observed certain changes in the liver after injections of ether or other lipid solvents, such as chloroform or carbon tetrachloride. There was a destruction of the mucosal lining of the gallbladder and biliary tract and edema of the hepatic parenchymal cells. Attempts to dissolve so-called mixed stones in rubber tubing were unsuccessful after fifteen days of continuous contact with the ether. Probstein and Eckert assumed that all of Pribram's cases were ones in which the stones were composed of pure cholesterol or at least were not covered with a layer of calcium and were therefore readily dissolved by ether. They stated the belief that a more likely explanation is that the mechanical effect of injections of ether was sufficient to dislodge the stones.

In a recent review of advances in the surgical treatment of biliary diseases, Boyce [10] gave ether credit for being a safer agent than Probstein and Eckert had indicated.

Raffl [3] also experimented on dogs and found that they objected strenuously to injections of ether through a cholecystostomy tube and that the size of stones placed in the gallbladder diminished slowly; it was only after four weeks of treatment had elapsed that the stones showed almost complete disintegration. The mucosa of the biliary tract was found intact even after a month of exposure to 3 cc. of ether twice daily. He has concluded that the use of ether in the dissolution of gallstones in vivo is a slow process and a dangerous one unless provision is made for immediate exit of the ether from the gallbladder or the ducts through a two way system. He considered the use of ether in dissolving gallstones a helpful procedure, alone or in conjunction with the biliary flush.

To summarize the experiments of surgeons who were using ether in dogs or patients, it may be said that the results were not very encouraging because (1) ether injections are painful unless special precautions are taken to avoid rapid increase of intraductal pressure, (2) the action of the injection is slow and not sufficiently strong and (3) there is a potential danger of damage to the liver or the extrahepatic ducts.

In search for a more effective solvent, our attention was focused on chloroform because it offers the following advantages: (1) its boiling point is 61 C. as compared with 35 C. of ether, which, obviously, is more volatile and therefore more apt to increase the intraductal pressure; (2) its solvent effect on cholesterol is much more pronounced than that of ether; (3) bile pigments are easily soluble in warm chloroform but only slightly soluble in ether, and (4) the solvent effect of chloroform can be considerably intensified by heating, while raising the temperature of ether would be ill advised on account of its inflammability. It may be mentioned here that both ether and chloroform are sterile.

EXPERIMENTS

To test the efficacy of chloroform, the following experiments were performed:

1. Cholesterol stones of equal size were placed into two test tubes, one filled with chloroform and the other with ether, and both tubes were agitated. After a few minutes practically no fragmentation was noticed in the tube filled with ether, while chloroform showed a slight solvent action. The effect of chloroform was, however, greatly intensified by heating; chloroform heated to about 38 C. (100.4 F.) caused a fragmentation and disintegration of stones within a few minutes. Contrary to this observation, the effect of ether was only slightly increased by heating.

The same experiments were repeated with pure pigment stones and with mixed stones consisting of cholesterol and pigment-calcium. Heated chloroform assumed a brownish color within a few minutes due to dissolution of bile pigments, and the stones disintegrated rapidly. On the other hand, the effect of heated ether was considerably less impressive.

In order to simulate conditions in vivo, a stone was placed into a translucent synthetic rubber tubing, producing a complete obstruction of it. The effect of the solvent under such experimental conditions was enhanced by gently squeezing the tubing and thus bringing the stone into closer contact with the fluid. The experiments demonstrated the superiority of warm chloroform over ether.

In the first series of experiments on animals, cholecystostomy was performed on 2 dogs, and two cholesterol and two mixed stones were placed into the gall-

6. Morton, H. B.: The Treatment of Common Duct Stone Missed at Operation, Surgery **12**:591, 1942.

7. Hunt, C. J.: Diagnosis and Management of Gallbladder Disease, J. Missouri M. A. **38**:46, 1941.

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10. Boyce, F. F.: Hepatic and Biliary Tract Disease, Ann. Surg. **109**:351, 1939.

bladder of each animal. After five days 3 to 4 cc. of chloroform heated to 38 C. (100.4 F.) was injected into the gallbladder of 1 animal, the other serving as control. A clamp was applied to the tube immediately after the injection and was left until the next day. The injections were repeated on five successive days, and the animals were killed three days after the last injection. While authors who experimented with ether injections remarked that the animals strongly objected to such procedures, no pain was noticed after injections of chloroform. The autopsy showed no effect of chloroform on the stones. This was probably due to the fact that chloroform was diluted with bile entering the gallbladder through the cystic duct; furthermore, the effect of chloroform could not be enhanced by a gentle massage of the stones or the overlying tissues.

In another series of experiments, cholecystotomy was performed on 4 dogs and various types of stones were placed in the cystic duct close to the junction with the common duct. Rubber tubing connected with a 5 cc. syringe was introduced into the cystic duct. The syringe was filled with 3 to 4 cc. of chloroform heated to 38 C. (100.4 F.), and the fluid was alternately injected and aspirated several times. After a few such maneuvers, the aspirated chloroform assumed a brownish color, and minute fragments of stones appeared in the syringe. The disintegration of the stones in the biliary duct could be greatly intensified and speeded up by a gentle squeezing of the duct in the region of impaction. After several injections and aspirations the stones disappeared from the duct. After the experiment the opening in the gallbladder was sutured, and the animals were killed two to six days later. The gallbladder, several sections of the liver from the hilus and more remote regions and also the pancreas and kidneys were removed for histologic examinations, which failed to reveal any pathologic changes except slight fatty deposits in the central half of the hepatic lobules, which were present also in control specimens.

Finally, 3 to 4 cc. of heated chloroform was injected into the cystic or the common duct of 5 dogs with the gallbladder intact, by means of a 5 cc. syringe with a tonsil needle attached. Two dogs were killed forty-eight hours later, 2 others five days, and 1 dog seven days after the injection. Gallbladder, bile ducts and several specimens of the liver close to the hilus and from more remote areas were removed for histologic studies. Corresponding organs of 2 normal dogs were used for comparison. The microscopic examination of the gallbladder showed a slight edema of the subserous layer, with a slight round cell infiltration of the remainder of the wall. The epithelium of the mucosa was well preserved. The epithelial lining of the bile ducts also had a normal appearance. Fatty changes in the central half of the hepatic lobules were found in all specimens, including those from the control animals. The changes were not more pronounced in the hilus region than in specimens taken from other areas of the liver. Therefore, a conclusion seems justified that injections of chloroform did not produce any demonstrable changes in the liver, the gallbladder or the extrahepatic ducts.

COMMENTS

Heated chloroform proved its superiority over ether in experiments in vitro as far as fragmentation and dissolution of gallstones is concerned and was found to cause no demonstrable damage to the liver or the extrahepatic biliary tract when injected into the common duct in experiments on dogs.

No experienced surgeon will contest the statement that once a stone is found in any portion of the extrahepatic biliary tract it can be removed manually by the customary methods, such as scooping, milking and flushing. However, injections of chloroform could be employed if the stone is lodged firmly in a pouch or diverticulum of the common duct and attempts to remove it by mechanical means encounter great difficulties or are likely to produce considerable trauma.

Repeated injections and aspirations of heated chloroform may advantageously be employed as a supplementary measure to mechanical maneuvers when the surgeon succeeds in crushing a lodged stone but is not sure that all fragments have been removed.

When a stone is lodged close to the terminal end of the common duct, injections of heated chloroform may be given a trial because, if successful, they will obviate the transduodenal approach, which is fraught with danger of infections and may offer considerable technical difficulties.

On rare occasions a stone in the hepatic duct may get away from the operator and slip into the liver. In such unfortunate cases, injections of chloroform may be tried.

As to the technic, a 5 cc. syringe with a cannula attached may be used for this purpose. To and fro motions of the piston will facilitate a fragmentation of the stones and dissolution of the debris. For safety's sake, the hepatic duct may be pinched with two fingers or clamped with rubber-covered prongs of a forceps to prevent chloroform from reaching the liver.

A gentle massage of the biliary duct over the stone will greatly contribute to the fragmentation of the calculus. A flushing of the biliary ducts with warm isotonic solution of sodium chloride should follow injections of chloroform in order to eliminate the danger of a possible toxic reaction.

Stones in the common duct may be overlooked at the operation and may cause clinical manifestations of obstruction later. Lahey[11] has repeatedly called attention to the frequency with which small stones low in the common duct were not found at operation. Best[12] noted that thorough exploration of the common duct by palpation, probing, scooping, irrigation and suction does not always verify the presence of stones.

11. Lahey, F. H.: The Incidence and Management of Stones in the Common and Hepatic Ducts, Ann. Surg. **98**:644, 1933.

12. Best, R. R.: Cholangiographic Demonstration of the Remaining Common Duct Stone and Its Nonoperative Management, Surg., Gynec. & Obst. **66**:1040, 1938.

He [13] introduced the "biliary flush," consisting chiefly of the use of glyceryl trinitrate, atropine and magnesium sulfate for relaxation of the sphincter of Oddi and sodium dehydrocholate to increase the secretion of bile. On one hand, this method is not always successful while, on the other hand, a secondary search for stones is connected with a high mortality. Therefore Pribram [6] offered as an alternative his method of repeated injections of ether. We are opposed to repeated injections of ether or chloroform during the postoperative period for patients with a T tube and signs of obstruction of the common duct for the following reasons: (1) The solvent would flow through the common duct in the direction of the least resistance, i. e., toward the liver and not toward the stone, so that its effect would be lost; (2) without a gentle massage of the region of impaction, the solvent effect of the fluid on the stone might not be sufficient, and (3) there is a potential danger of a toxic effect of repeated injections of chloroform on the liver.

SUMMARY

As a rule, mechanical means are sufficient for the removal of stones from the biliary tract. Therefore the field of usefulness of a chemical solvent is so limited that only two indications can be suggested:

1. When a stone is firmly lodged in the common duct and cannot be removed manually or when the surgeon is not certain that all broken particles of the stone have been removed. If the stone is firmly lodged close to the ampulla of Vater, the use of a solvent may obviate the necessity of opening the duodenum.

2. When a stone in the hepatic duct slips away into the liver in course of attempts to remove it mechanically.

In such circumstances injections of heated chloroform may be given a trial, because apparently this method does not represent a therapeutic hazard. To play safe, it is advisable to use not more than 5 to 6 cc. of the solvent and to pinch the hepatic duct during the procedure. In experiments in vitro as well as on animals, heated chloroform proved to be superior to ether as an efficient solvent for gallstones.

Repeated injections of chloroform during the postoperative period should be discouraged because they are not efficient and represent a potential hazard.

Final evaluation of the method requires further observations.

13. Best, R. R., and Hicken, N. F.: Nonoperative Management of Remaining Common Duct Stone, J. A. M. A. **110**:1257 (April 16) 1938. Best.[12]

CLEANSING OF OIL-COVERED SKIN AND BURNS

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In this investigation a survey of the effectiveness of surface-active agents for the removal of heavy oils and tars from intact and from injured skin has been carried out. At the present time, a large number of surface-active agents are commercially available. These many compounds and mixtures have in common the power to modify the properties of surfaces but vary widely in specific modes of surface activity, such as wetting power, emulsifying power, and dispersing, penetrating and foaming action, not only with respect to any specific system of surfaces but also from one system to another.

If the living skin is considered a component of such a system of surfaces, the pertinent powers of surface-active agents may in general be taken to vary between wetting power, on the one hand, and emulsifying power, on the other, although these do not necessarily oppose each other. The former is a measure of the ability of a compound to lower interfacial tension; the latter, a measure of ability of a compound to prevent the breaking of an emulsion. The dermatologically important property of detergency is a combination of these powers and is not necessarily parallel to either. Sodium dioctylsulfosuccinate (Aerosol OT) is an excellent wetting agent but not so good an emulsifying agent. Sodium kerylbenzenesulfonate (Nacconol) is both a good wetting agent and a good detergent, while the cation-active invert soap cetyldimethylbenzylammonium chloride (Triton K-60) is an excellent emulsifying agent but of limited powers as a wetting agent or as a detergent. Sodium lauryl sulfate (Duponol) is an excellent detergent and a fair wetting agent; sodium stearate (common soap) is a poor wetting agent but an excellent detergent. In any case, it is evident that "detergent" is too general a term for the substances involved. They are better classified as "surface-active agents," and at present they may be regarded as falling into the following chemical types (for a more complete review of this topic, see Snell [1]).

1. Alkali salts of long chain fatty acids, e. g., ordinary soap.

2. Alkali salts of sulfated long chain fatty alcohols (e. g., sodium lauryl sulfate, Duponol), esters (e. g., sodium glyceryltriricinoleate sulfate, sulfated castor oil) and amides (e. g., sodium N-oleyl taurate, Igepon T).

3. Alkali salts of long chain fatty sulfonic acids (e. g., sodium petroleum sulfonate, SP 315).

4. Alkali salts of alkylaryl sulfonates (e. g., sodium kerylbenzenesulfonate, Nacconol).

5. Polymerized ethers, esters and alcohols (e. g., the polyoxyalkylene ether of partial lauric acid esters, Tween).

6. Acid salts of quaternary ammonium bases, cation-active "invert soaps" (e. g., cetyldimethylbenzylammonium chloride, Triton K-60).

The specific requirements of any instance in which surface-active agents are to be used thus should dictate which special set of properties is to be sought. In this study an attempt has been made to determine which surface-active agent or agents and in what forms would best serve to remove heavy oils and tars from intact and from damaged skin. All the products listed in a compilation appearing in the January 1943 issue of *Industrial and Engineering Chemistry*, entitled "Surface-Active Agents Manufactured in the United States and Commercially Available," were requested from their manufacturers. Those received, together with some common surface-active agents not listed and some of those recently developed but not listed, were submitted to test. These totaled one hundred and sixty-five substances, and each was tested in a variety of forms and according to several criteria of excellence.

Initial results corroborated those reported by Rosenberg [2] and Schwartz [3]: When light oils con-

From the Dermatoses Section, Industrial Hygiene Division, Bureau of State Services.

1. Snell, F. D.: Indust. & Engin. Chem. **35**:107, 1943.
2. Rosenberg, N.: Surgery **13**:385, 1943.
3. Schwartz, L.: Pub. Health Rep. **56**:1788, 1941.

taminate the skin and scrubbing is not a serious drawback, the mixtures listed by them were found to be suitable cleansers[4]; however, for highly adherent and viscous oils, the amount of mechanical action required by these and many other direct mixtures of surface-active agents became inordinate. For this reason, the investigation was directed toward the formulation of a mixture which would remove heavy oils from the intact skin with a minimum of scrubbing and which would remove them from burned areas with no scrubbing action whatever when used in the form of a wet dressing.

On the principle of *similia similibus solvuntur,* liquid petrolatum was made the solvent base for the mixtures of surface-active agents then tested. A further basis for the use of liquid petrolatum in this manner exists in the numerous clinical reports of its use as a dressing for burns. All agents received were prepared as 30 per cent mixtures in liquid petrolatum U. S. P. and, when indicated, dilutions of 20 per cent and 10 per cent were also prepared, as well as the corresponding dilutions in light liquid petrolatum U. S. P. Many of the mixtures so obtained

Fig. 1.—Materials necessary for the "dressing test" (test 2). The gauzes were prepared by anchoring cotton tapes to the backs of the patches with adhesive plaster.

were immediately discarded on physical grounds, e. g., immiscibility of the components or high viscosity. In general, only two physical states were found acceptable: stable emulsions and clear solutions of low viscosity, although all mixtures bordering on these states were also subjected to test.

Two tests for comparative activity were employed. The first consisted in placing a 1 inch (2.5 cm.) disk of medium fuel oil about 3 mm. deep on the palm of the hand and pouring over this 2 cc. of the surface-active agent–petrolatum mixture. The rate of mixing of the two layers was observed; then, by rubbing the patch of oil lightly with a single finger for fifty rotations the two were mixed, and the physical character of the mixture observed. The palm was then

Fig. 2.—Appearance of the test sight after application of standard patch of oil, prepared by inverting the bottle for thirty seconds over each site, reinverting the arm and bottle and rapidly removing the bottle from the arm.

washed with a stream of cold water and the rate of removal of the mixture observed. Those petrolatum mixtures which were slow to mix with the fuel oil or which, having been mixed with it, were resistant to water and left an oily stain on the skin were discarded. The test was regarded as a measure of detergency.

The second test consisted in essence of overlaying a disk of very heavy fuel oil with a surgical gauze sponge (Johnson and Johnson, 2 by 2 inches [5.8 cm.], twelve ply) soaked with 2 cc. of the petrolatum mixture (figs. 1, 2 and 3). The dressing was kept in place with cotton tapes loosely tied and allowed to remain for one-half hour. At the end of this period, it was removed and the oil spot examined for residue and for the ease of its removal with gentle swabbing and with a stream of cold water. Both petrolatum-soaked gauze and dry gauze were used as controls, and it may be mentioned that while these control

4. These were: (Schwartz) sulfated castor oil with 2 per cent Santomerse, Duponol, or Igepon; and (Rosenberg) (1) Sulfatate, 9 parts, Atlas G772S, 1 part; (2) Sulfatate, 11 parts, Aerosol OT 25 per cent aqu., 1 part; (3) Sulfatate, 19 parts, Orvus, 1 part; (4) Sulfatate, 49 parts, Tergitol 4, 1 part; (5) Sulfatate, 6 parts, turkey red oil, 5 parts, Aerosol OT 25 per cent aqu., 1 part; (6) turkey red oil, 11 parts, Aerosol OT 25 per cent aqu., 1 part.

dressings removed the major part of the oil, they left deep brown oily stains on the skin. The mixtures which demonstrated superiority in this test were then subjected to others in which the period of contact between the oil and the dressing was reduced to fifteen minutes or in which successive dressings of fifteen minutes on the same oil patch were employed. Each mixture was tested in triplicate. This test was regarded as a measure of the ability of the surface-active agent mixture to facilitate the removal of oil from the skin with minimum mechanical action.

Of the one hundred and fifty-nine mixtures of surface-active agents with liquid petrolatum which met the physical standards required of these preparations (see preceding paragraphs), twenty were found to be superior detergents for the removal of oil from the intact skin (table 1). All but one (*9C*) were emulsions, and it was observed that in general when oil-soluble surface-active agents were applied in this test thin films of petrolatum were left on the skin. Since the agents of this type tend to produce water in oil emulsions, it is clear that the skin remains in contact with a continuous oily phase and that flushing with water serves only to remove the upper layers of the emulsion. "Superfatting" in this sense has a sound physical basis. Surface-active agents which produced clear solutions in liquid petrolatum are listed in table 2.

With two exceptions, the mixtures of the surface-active agents with heavy and with light liquid

TABLE 1.—*Mixtures of Surface Active Agents (30 per Cent) and Liquid Petrolatum Which Were Superior Detergents*

Number	Type of Compound	Commercial Name	Company
8	Isopropyl naphthalene sulfonate	Aerosol OS	American Cyanamid and Chemical Corp.
9C	Dioctyl sodium sulfosuccinate	Aerosol OT	American Cyanamid and Chemical Corp.
11A	Alkyl aryl sulfonate	Aheowet L-MA	Hoffman-La Roche, Inc.
32	Monobutylphenylphenol sulfonate	Areskap 50	Monsanto Chemical Co.
635	Alkyl sulfate	L-144-WD	E. I. DuPont De Nemours & Co., Inc.
636	Alkyl sulfate	LS paste	E. I. DuPont De Nemours & Co., Inc.
631O	Alkyl sulfate	WS	E. I. DuPont De Nemours & Co., Inc.
71	Polyether alcohol condensate	Igepal CA	General Dyestuff Corp.
109	Nonionic fatty acid condensate	Neutronyx	Onyx Oil & Chem. Co.
110	Acid alkylolamine condensate	Ninol 737	Ninol Laboratories
155	Alkylaryl amine sulfonate	Santomerse D	Monsanto Chemical Co.
158	Alkylaryl sulfonate	Solvadine NC CON	Ciba Pharmaceutical Products, Inc.
158B	Alkylaryl sulfonate	Solvadine AL	Ciba Pharmaceutical Products, Inc.
161E	Sorbitan monolaurate	G-1020	Atlas Powder Company
161D	Sorbitan monolaurate	G-1030	Atlas Powder Company
167	Dioctyl ester of sodium sulfosuccinic acid	Stablex C	Heveatex Corp.
217	Not divulged	Neccol NS	General Dyestuff Corp.
221	Dimethylalkylamine oxide	Ammonyx	Onyx Oil & Chem. Co.
224	Trialkyl ammonium bromide	Quarto	Onyx Oil & Chem. Co.
233	Trialkyl amine oxide	Ammonyx CO	Onyx Oil & Chem. Co.
235	Not divulged	Aromine PM	Berkshire Chemical Co.
236	Alkylaryl sulfonate	Penetrator 394A	Laurel Soap Mfg. Co., Inc.

TABLE 2.—*Surface-Active Agents Which Formed Solutions with Liquid Petrolatum (30 per Cent Unless Otherwise Noted)*

Number	Type of Compound	Commercial Name	Company
9C	Dioctyl sulfosuccinate (10 per cent)	Aerosol OT	American Cyanamid and Chemical Corp.
35	Anhydrohexitol oleate	Arecal C	Atlas Powder Company
62B	Sulfonated petroleum (10 per cent)	Dipex	Stanco Incorporated
62C	Sulfonated petroleum	Dipex	Stanco Incorporated
638	Alkyl sulfate	Duponol OS	E. I. DuPont De Nemours & Co., Inc.
105	Cation-active amine esters of fatty acids	Negamine 142	Synthetic Chemicals, Inc.
112	Hexitan fatty ester	NNO	Atlas Powder Company
158	Alkylaryl sulfonate	Solvandine S	Ciba Pharmaceutical Products, Inc.
161	Sorbitan monolaurate	Span 20	Atlas Powder Company
161A	Sorbitan laurate	G-630	Atlas Powder Company
163	Sorbitan stearate	Span 60	Atlas Powder Company
164	Sorbitan monoleate	Span 80	Atlas Powder Company
165	Sorbitan trioleate	Span 85	Atlas Powder Company
216	Not divulged	Emulsifier 71	Victor Chemical Works
227	Not divulged	NNO	Atlas Powder Company
231	Not divulged	Emulsifier 67	Victor Chemical Works
232	Polyalkyl phosphate	Emulsifier 20	Victor Chemical Works
280	Triisopropanol ammonium oleate (10 per cent)		

petrolatum failed to show satisfactory activity in the dressing test. The two exceptions were solutions of Emulsifier 20 and Aerosol OT in light liquid petrolatum. In these cases, effectiveness increased with concentration up to 30 per cent and 10 per cent respectively, then dropped until the pure Emulsifier 20, for example, showed little power to aid the removal of the fuel oil in the dressing test. It may be noted that with the sole exception of the dioctyl ester of sodium sulfosuccinic acid (Aerosol OT) no surface-active agent was able to parallel its performance in tests 1 and 2. That is, a number of detergent mixtures which were efficient for scrubbing fuel oil from the skin (see table 1) gave poor results in the dressing test. Conversely, while the solutions of surface-active agents in liquid petrolatum in general were poor detergents, they proved in

Fig. 3.—Appearance of the sites during the test. Each mixture subjected to test 2 was tested in triplicate.

general more effective in the dressing test, although with the two exceptions noted these solutions tended to leave water-resistant films of petrolatum on the skin.

In the light of these observations, an effort was made to combine the properties of the two types of surface-active agents. The members of each group were systematically tested in combination as solutions in light liquid petrolatum. Three of these combinations proved to be outstandingly effective reagents for the dressing test in that three fifteen minute dressings (test 2) produced skin surfaces much cleaner than either the dry or the wet controls, e. g., mixtures 258, 263 and 266 (see the following tabulation). Mixture 263 was distinctly superior. Nevertheless, they remained inferior detergent mixtures, i. e., failing in the scrubbing test (test 1).

Mixture		Parts
258	Light liquid petrolatum U. S. P.	50
	Aerosol OT solid	3
	Duponol OS	15
263	Light liquid petrolatum U. S. P.	50
	Stablex C	3
	Emulsifier 20	15
266	Light liquid petrolatum U. S. P.	50
	Penetrator 394 A	3
	Emulsifier 20	15

Reviewing the results as a whole, we found that the petrolatum solutions of only one substance, the dioctyl ester of sodium sulfosuccinate, proved superior in both the detergency test and the dressing tests. Since the chronic toxicity of Aerosol OT has been demonstrated to be of a low order,[5] and since in our trials there was no evidence of irritation of the skin from its mixtures with liquid petrolatum, it meets the physiologic as well as the physical requirements. Thus, a 10 per cent solution of dioctyl sodium sulfosuccinate in light liquid petrolatum was the best agent for the cleansing of oil-covered or tar-covered skin. This solution is prepared by warming a stirred mixture of solid Aerosol OT with light liquid petrolatum to 95 to 100 C. This mixture has also been found to be of value in removing the scales of psoriasis and seborrhea from the skin and the scalp. It is also suggested as a vehicle for such medicaments as dihydroxyanthranol and chrysarobin.

SUMMARY

In this investigation of the cleansing of oil-covered skin and burns, one hundred and sixty-five surface-active agents manufactured in the United States and commercially available were systematically studied. Some three hundred and fifty mixtures of single surface-active agents or surface-active agents in combination with both light and heavy liquid petrolatum (purified mineral oil) were the subjects of approximately seven hundred tests of comparative activity in removing heavy fuel oil and tar from the skin. The test oils employed were heavy and light fuel oils. Three mixtures of surface-active agents were found capable of completely removing heavy fuel oil without ostensible mechanical action in the course of three fifteen minute applications on surgical gauze but were also found to have poor detergency. Dioctyl sodium sulfosuccinate in 10 per cent light liquid petrolatum solution had good detergency and high activity as an oil remover in dressing form.

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NITROGEN BALANCE STUDIES ON SURGICAL PATIENTS RECEIVING AMINO ACIDS

OBSERVATIONS ON PATIENTS WITH OBSTRUCTING LESIONS OF THE ESOPHAGUS AND STOMACH RECEIVING AMINO ACIDS BY PARENTERAL INJECTIONS AS THE EXCLUSIVE SOURCE OF PROTEIN

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In the six years that have elapsed since Elman and Weiner [1] first succeeded in giving amino acids intravenously to human beings, the parenteral administration of amino acids in the form of specially prepared protein hydrolysates has become an established clinical procedure. This has been particularly true in the management of cases of gastrointestinal diseases in which the existence of protein deficiency is usually easily recognized and in which the possibility of oral alimentation is limited or impossible. At first glance the nutritional value of such a method of feeding would appear obvious. However, many factors are involved in its successful application. Even though the products available for parenteral use are derived from nutritionally good proteins, it is not safe to assume them to be adequate until they are proved by proper studies under controlled conditions to be able to provide nitrogen balance. Also, it is necessary to recognize the quantities of amino acids needed for the particular patient, the adjuvant requirements of carbohydrate, minerals and vitamins, the best method of administration and the limitations of the efficacy of such management even under the best of conditions. The present report is a part of an investigation to determine some of these factors.

PLAN OF STUDY

To study the adequacy of therapy with parenteral injections of amino acid, a series of cases of obstructive lesions of the esophagus and stomach was chosen. This type of case presents a severe nutritional challenge to the clinician. The patients were predominantly men of 50 years or older, unable to eat solid food for weeks or months and often unable to retain liquids. Their teeth and gums were in poor condition. Because of frequent vomiting, many of them were considerably dehydrated. Their fat stores were for the most part depleted. The average loss in weight was 36 pounds (16.3 Kg.). More than 40 per cent of these patients had secondary anemia on admission to the hospital. In others the anemia became manifest after fluid and salt had been administered. The incidence of hypoproteinemia in these patients was 50 per cent, much higher than the 23 per cent reported from this institution [2] for the general variety of patients with surgical lesions. Here, again, the incidence would probably have been still higher if it had been redetermined after hemoconcentration had been eradicated by administration of fluid and salt. That such patients do not tolerate operations well has been fully demonstrated in a review of 80 cases of gastrostomy performed at the Cook County Hospital between 1941 and 1944.[3] Of the 80 patients operated on, 43 died within two months, a good portion of these during the first week. The nutritional status of such patients is difficult to improve unless one resorts to parenteral feeding. The clinical evaluation of the results of such a nutritional program instituted for them is likely to be unequivocal. Also, since the intake of amino acids can be accurately determined and since the number of stools to be analyzed is small, it is relatively easy to make accurate nitrogen balance studies on these patients in surgical wards.

Nitrogen balance studies conducted in this series of cases permit the evaluation of the adequacy of the amino acid preparations used, for if any of the essential amino acids are not present in sufficient amounts a positive nitrogen balance will not be obtained except with extraordinarily large quantities of the preparation.[4] Furthermore, they allow the recognition of the

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unusually large nitrogen losses occurring at times before or after operations, losses which can be prevented by correspondingly large intakes. If such balance studies are carried out during a control period, some idea will be obtained of the previous nitrogen losses and of the degree and the duration of positive nitrogen balance required for complete restitution of the protein stores. Also, such studies may reveal relative improvement in nitrogen balance, even if an absolute positive balance is not obtained.

In 11 of the 14 cases reported, the amino acid preparation used was Parenamine (Stearns).[5] When the preparation was given intravenously, 300 cc. (or 45 Gm. of amino acids, containing 6 Gm. of nitrogen) was diluted with 700 cc. of sterile 5 per cent dextrose solution or isotonic solution of sodium chloride and injected at a rate of 350 cc. per hour.

ministration was to add 500 cc. of Cutter's solution to 500 cc. of 10 per cent dextrose or isotonic saline solution. A liter of this mixture furnished 4.25 Gm. of nitrogen.

Both Parenamine and Cutter's amino acids were administered to all patients without untoward reactions. Previous physiologic studies[7] had demonstrated that when amino acids were injected intravenously at rates of 10 to 25 Gm. per hour plasma amino acid nitrogen levels rose from an average of 5 mg. per hundred cubic centimeters to not more than 9 mg. Only when the rate of administration was greater than this did the concentration rise to 10 to 12 mg. per hundred cubic centimeters. At this level, nausea and vomiting occurred frequently.

The usual procedure involved a control study of the nitrogen excretion when the patient was getting only

Summary of Nitrogen Balance Studies for Fourteen Patients with Obstructive Lesions of the Esophagus and Stomach Treated with Parenteral Amino Acids as the Exclusive Source of Protein

Case	Age	Color	Diagnosis	Control Average Daily Nitrogen Balance, Gm. N	Daily Dose of Amino Acids, Gm.		Length of Administration, Days	Average Daily Nitrogen Balance, Gm. N	Total Nitrogen Balance for Period of Amino Acid Administration, Gm. N	Hematocrit, %		Serum Protein, Gm./100 Cc.		Serum Albumin, Gm./100 Cc.		Change in Wt., Lb.	Preparation of Amino Acid Used
					AA	N				Initial	Final	Initial	Final	Initial	Final		
1	72	W	Paraesophageal Hernia	.....	60	8	8	+2.1	+17.0	35	37.5	6.0	6.7	3.5	3.8	+3	Parenamine
					90	12	12	+4.5	+54.1								
2	62	W	Carcinoma of Esophagus	— 4.7	60	8.5	11	+0.43	+ 4.8	50	37	5.4	5.9	2.9	3.6	—2	Cutter's
					90	12.75	6	+3.4	+20.2								
3	72	W	Carcinoma of Stomach	— 8.8	60	8	11	—0.75	—8.09	39	34	5.7	5.4	3.3	3.2	0	Parenamine
					90	12	4	+2.1	+8.03								
4	60	W	Carcinoma of Esophagus	— 5.8	90	12	12	—0.90	—11.1	37	34	6.4	6.4	3.7	3.9	+5	Parenamine
					135	18	10	—2.0	—20.3								
5	64	N	Carcinoma of Esophagus	— 4.9	60	8	7	+2.1	+14.7	41	31	6.9	6.2	4.4	3.5	+4	Parenamine
					90	12	13	+3.8	+41.5								
6	60	W	Carcinoma of Esophagus	—10.0	60	8.5	8	—2.5	—18.9	43	37	6.5	6.2	4.2	4.1	+3.5	Cutter's
					120	17	11	+0.27	+ 3.0								
7	62	W	Carcinoma of Esophagus	— 7.0	60	8	7	—2.2	—15.7	45	39.5	7.1	6.4	4.4	4.1	+3	Parenamine
					120	16	6	+5.6	+33.5								
8	54	W	Carcinoma of Esophagus	— 2.3	60	8	7	+1.45	+10.2	31	23	6.8	5.5	4.2	2.8	+2	Parenamine
					90	12	8	+3.8	+30.4								
9	56	W	Carcinoma of Stomach	— 4.5	60	8	5	+1.3	+ 6.3	43	38	7.5	5.9	4.3	3.8	—2	Parenamine
					90	12	5	+2.0	+10.0								
10	48	W	Carcinoma of Stomach	— 7.2	120	16	15	+3.3	+39.5	28	32	5.3	7.0	3.5	4.0	+1	Cutter's
11	73	W	Carcinoma of Stomach	— 2.1	60-90	8-12	9	0	— 0.20	40	26.5	5.8	6.5	3.4	3.7	0	Parenamine
					120	16	6	+3.9	+23.5								
12	64	W	Carcinoma of Stomach	—10.4	90	12	8	+2.7	+21.6	33	26	5.6	5.6	3.1	3.3	0	Parenamine
13	66	W	Carcinoma of Esophagus	— 3.8	120	16	4	+5.0	+20.1	40	41	5.2	4.4	3.0	2.7	0	Parenamine
14	63	W	Carcinoma of Esophagus	— 7.0	120	16	5	+4.7	+23.4	41	40	5.6	5.0	3.4	3.2	0	Parenamine

The amino acid preparation used in the 3 other cases was Cutter's amino acids.[6] Our usual method of administration was to add 500 cc. of Cutter's solution to 500 cc. of 10 per cent dextrose or isotonic saline solution. A liter of this mixture furnished 4.25 Gm. of nitrogen.

Both Parenamine and Cutter's amino acids were administered to all patients without untoward reactions. Previous physiologic studies[7] had demonstrated that when amino acids were injected intravenously at rates of 10 to 25 Gm. per hour plasma amino acid nitrogen levels rose from an average of 5 mg. per hundred cubic centimeters to not more than 9 mg. Only when the rate of administration was greater than this did the concentration rise to 10 to 12 mg. per hundred cubic centimeters. At this level, nausea and vomiting occurred frequently.

The usual procedure involved a control study of the nitrogen excretion when the patient was getting only carbohydrate, isotonic saline solution and parenterally injected vitamins. After two to five days on this control regimen, the patient was given amino acids intravenously in quantities determined during the control excretion. On occasion, subcutaneous, intrasternal or transgastric routes were utilized, the last postoperatively with the aid of an Abbott-Rawson tube. An effort was made in each case to meet the minimal caloric requirements of the patient by giving sufficient carbohydrate, thereby sparing the amino acids for regeneration of tissue and plasma protein. This attempt was usually successful if liquids could be given by mouth. Orange juice containing Cartose[8] furnished a considerable portion of the carbohydrate; the remainder was given intravenously. When fluids could not be given by mouth, the problem of providing adequate quantities of dextrose intravenously was usually

5. Parenamine was furnished by Frederick Stearns & Company, Detroit. It is marketed as a sterile 15 per cent solution of amino acids prepared by acid hydrolysis of casein. It contains, in addition to the amino acids obtained from the casein, 1 per cent of synthetic *d,l*-tryptophan, to replace that which was destroyed during the acid hydrolysis. The amino acid content of this product has recently been determined by Block (Block, R. J., and Bolling, D.: Essential Amino Acid Distribution in a Casein Hydrolysate Suitable for Parenteral Injection, Am. J. Pharm. **116:** 368, 1944).

6. Cutter's amino acids, furnished by Cutter Laboratories, Berkeley, Calif., are prepared from fish protein by acid hydrolysis. The preparation has been found by us through experiments on both animals and human beings to be free of pyrogens and other toxic products. It is put up in a 6 per cent solution in distilled water in 250 cc. bottles, which can be used directly for parenteral administration.

7. Hoffman, W. S., and Kozoll, D. D.: Blood Changes Following Administration of Protein Hydrolysates, Federation Proc., to be published.

8. Furnished by Scientific Sugars Company, Columbus, Ind.

insurmountable. By the injection of 4 liters of fluid daily, which required twelve to fourteen hours, it was possible to furnish 105 to 150 Gm. of dextrose, 90 to 135 Gm. of amino acids and 9 Gm. of sodium chloride. The potential caloric value of such a diet was 780 to 1,140 calories, but if the amino acids were to be used for synthesis of protein only 420 to 600 calories was available. Even this limited program required that 3 of the 4 liters of fluid be hypertonic, and when the use of so much hypertonic fluid persisted for several weeks thrombosis of all the available veins was frequently produced. For this reason intravenous injections were always given in the most distally available portion of a vein, as in the wrist, and then progressively cephalad.

Vitamin B complex and vitamin C were given daily by subcutaneous injection.[9] The quantities given were believed to be adequate for the daily requirement.

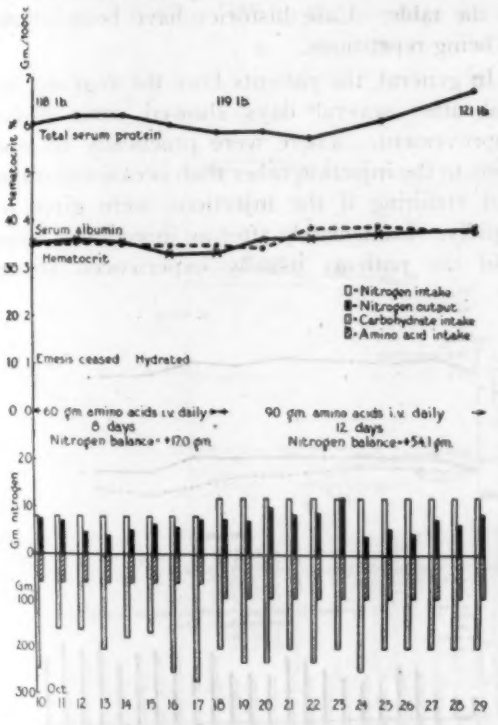

Fig. 1 (case 1).—Nitrogen balance study in a case in which the initial serum total protein level was 6 Gm. per hundred cubic centimeters, the serum albumin level was 3.5 Gm. and the hematocrit reading was 35 per cent. The patient was given 60 Gm. of amino acid (Parenamine) daily intravenously (8 Gm. of nitrogen per day) as the sole source of protein, with resulting positive nitrogen balance of 17 Gm. for eight days, or slightly better than 2 Gm. per day. In the ensuing twelve days the dose of amino acids per day was increased to 90 Gm. (12 Gm. of nitrogen), and a positive nitrogen balance of 54.1 Gm. was achieved, averaging 3.4 Gm. per day. The serum total protein level had risen to 6.7 Gm. per hundred cubic centimeters, the serum albumin level to 3.8 Gm. and the hematocrit reading to 37.5 per cent. The patient showed pronounced clinical improvement and underwent repair of a diaphragmatic hernia without event.

9. The products used were Betasynplex and Cantaxin, furnished by the Winthrop Chemical Company.

The following analyses were carried out: Hematocrit readings and sedimentation rates were determined by the method of Wintrobe,[10] hemoglobin by the photoelectric method of Sheard and Sanford[11] and protein nitrogen by the titrametric micro-Kjeldahl method.[12]

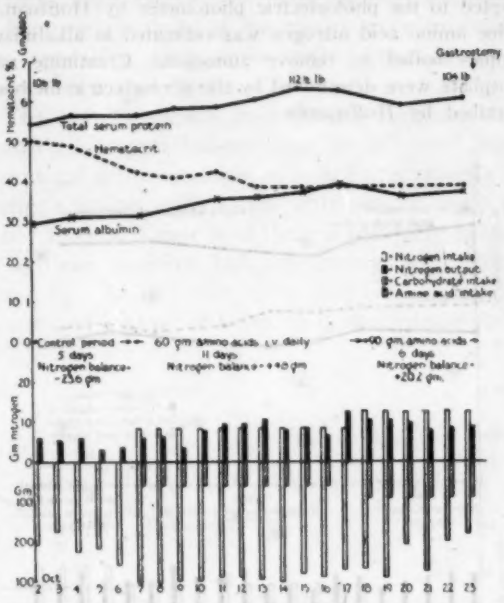

Fig. 2 (case 2).—Nitrogen balance study in a case in which the daily control nitrogen loss was 4.7 Gm., the control serum protein level 5.4 Gm. per hundred cubic centimeters, the albumin level 2.9 Gm. and the hematocrit reading 50 per cent, indicating a severe degree of protein deficiency and dehydration. On a regimen of 60 Gm. amino acids (Cutter's) given intravenously daily, the patient achieved a positive nitrogen balance of 4.8 Gm. for eleven days. The serum proteins rose to 6 Gm. per hundred cubic centimeters and the serum albumin to 3.6 Gm. while the hematocrit value fell to 37 per cent, suggesting that a 6.5 pound (2.95 Kg.) gain in weight might be due to tissue hydration. When the amino acid intake was increased to 90 Gm. per day (12 Gm. of nitrogen), the positive nitrogen balance rose to 20.2 Gm. for six days, or an average of 3.35 Gm. per day. At the conclusion of the study, serum proteins were 5.9 Gm. per hundred cubic centimeters, serum albumin 3.6 Gm. and hematocrit reading 37 per cent. At operation an extensive carcinomatosis was found.

One ampule of Betasynplex, containing 10 mg. thiamine hydrochloride, 5 mg. riboflavin, 5 mg. pyridoxine hydrochloride, 5 mg. calcium panthothenate dextrorotatory and 50 mg. nicotinamide and one ampule of Cantaxin containing 100 mg. of ascorbic acid were injected daily.

10. Wintrobe, M. M., and Landsberg, J. W.: Standardized Technique for Blood Sedimentation Test. Am. J. M. Sc. **189**:102, 1935.

11. Sheard, C., and Sanford, A. H.: A Photoelectric Hemoglobinometer: Clinical Application of the Principles of Photoelectric Photometry to the Measurement of Hemoglobin, J. Lab. & Clin. Med. **14**:588, 1929.

12. Ma, T. S., and Zuazaga, G.: Micro-Kjeldahl Determination of Nitrogen: A New Indicated and an Improved Rapid Method, Indust. & Engin. Chem. **14**: 280, 1942.

Serum total protein was further routinely checked by the falling drop method of Barbour and Hamilton,[13] results of which usually agree remarkably well with those of the Kjeldahl method. Plasma amino acid nitrogen was determined by the naphthoquinone method, adapted to the photoelectric photometer by Hoffman.[14] Urine amino acid nitrogen was estimated in alkalinized samples boiled to remove ammonia. Creatinine and phosphate were determined by the photoelectric methods described by Hoffman.[15]

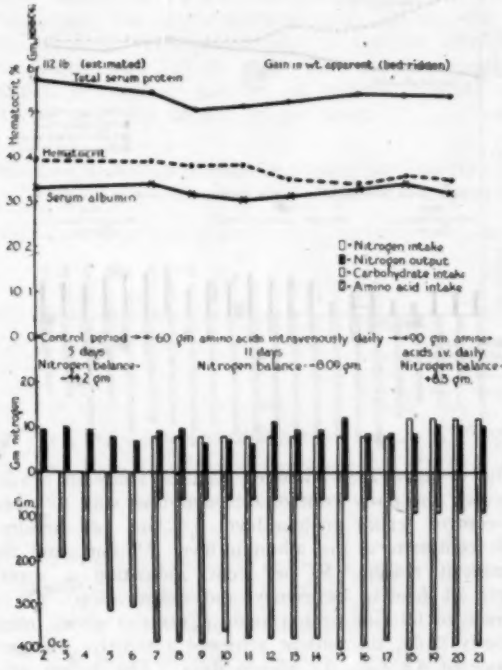

Fig. 3 (case 3).—Nitrogen balance study in a case of carcinoma of the cardia of the stomach in which the daily nitrogen loss during the control period was 8.8 Gm., the serum protein level 5.7 Gm. per hundred cubic centimeters, the serum albumin level 3.3 Gm. and the hematocrit value 39 per cent. When 60 Gm. of amino acids (Parenamine) was injected intravenously per day for eleven days, a negative nitrogen balance of 0.75 Gm. per hundred cubic centimeters resulted, with a decline in serum protein, albumin and hematocrit value. When 90 Gm. of amino acids per day was given, a positive nitrogen balance of more than 2 Gm. per day was achieved. The final serum protein level was 5.4 Gm. per hundred cubic centimeters and the serum albumin 3.2 Gm., but the decline in the hematocrit value to 34 per cent could explain the drop in protein concentration as due to an increase in plasma volume.

13. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity, J. Biol. Chem. **69**:625, 1926.

14. Hoffman, W. S.: A Photometric Adaptation of the Folin Method for the Determination of Plasma Amino Acid Nitrogen, Am. J. Clin. Path., to be published.

15. Hoffman, W. S.: Photometric Clinical Chemistry, New York, William Morrow & Company, 1941.

Analyses of stools were not performed as a routine procedure after it was established that the patients in this series had bowel movements on an average of once a week and that these stools seldom contained more than 1 Gm. of nitrogen, thus averaging less than 0.2 Gm. daily. When the analyses were performed, the stools were placed in large beakers, covered with about 300 cc. of water and treated with stirring under a hood with about 400 cc. of concentrated sulfuric acid. The charred homogenized mixture was cooled and made up to a liter, and an aliquot was analyzed for nitrogen.

RESULTS AND COMMENT

The results pertinent to nitrogen metabolism in 10 of the 14 cases are given in some detail in figures 1 to 10. All 14 cases are summarized in the table. Case histories have been omitted as being repetitious.

In general, the patients bore the regimen well and after several days showed some clinical improvement. There were practically no reactions to the injection other than occasional nausea and vomiting if the injections were given too rapidly. Immediately after an injection of amino acid the patients usually experienced an un-

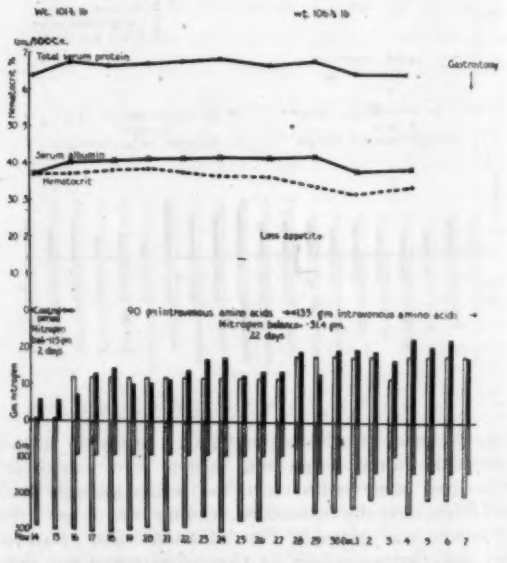

Fig. 4 (case 4).—Nitrogen balance study in a case of carcinoma of the esophagus with a control nitrogen loss of 5.75 Gm. per day, serum protein level of 6.4 Gm. per hundred cubic centimeters, serum albumin level of 3.7 Gm. and hematocrit value of 37 per cent. With intravenous injections of amino acids (Parenamine) of 90 Gm. per day (12 Gm. of nitrogen), a daily negative nitrogen balance of 0.85 Gm. per day was produced. A 5 pound (2.3 Kg.) gain in weight and rise in serum protein and albumin vouched for the clinical improvement seen in this case. With injection of 135 Gm. of amino acids daily (18 Gm. of nitrogen), a negative nitrogen balance of better than 2 Gm. per day still persisted. The serum protein level at this time was 6.4 Gm. per hundred cubic centimeters, serum albumin level 3.9 Gm. and hematocrit value 34 per cent.

pleasant sense of fulness, as after a full meal. But this lasted only for an hour or two. If vomiting preceded therapy, it usually abated after a few days of amino acid therapy and the patient expressed a desire for oral feeding. Subcutaneous and intrasternal infusions were not tolerated so well as intravenous injection, because of local pain. However, in no case was there any slough or other sign of local damage. Intragastric feeding through a gastrostomy opening was also successful, as was transgastric feeding immediately postoperatively through an Abbott-Rawson tube.

The daily nitrogen excretion in the control periods ranged from 2.25 to 10.4 Gm., the average being 6 Gm. While this average value is of the order usually obtained in starvation, it is probably a coincidence, for there were 3 cases of unusually low excretion, 2 to 3 Gm. daily, and 2 of rather large excretions, 10 Gm. daily. Subjects who have lost a great deal of weight would be expected to show a minimal nitrogen excretion (2 to 3 Gm. per day) if their fat stores were plentiful and if at least 50 per cent of their caloric requirements were met by carbohydrate intake. In those cases in which 200 to 300 Gm. of carbohydrate was furnished, there was indeed a tendency toward low nitrogen excretion. In the cases in which there were higher excretions, factors other than inadequate intake of carbohydrate or the lack of fat stores were probably also operative, such as excessive breakdown of tissue due to carcinoma.

The results shown in the table indicate that positive nitrogen balance can be achieved with parenteral administration of both Parenamine and Cutter's amino acids as the only source of nitrogen. In only 1 case was there a complete failure to achieve positive balance during any period (case 4). In this case, even 135 Gm. of Parenamine and 200 to 250 Gm. of carbohydrate daily were inadequate. In other cases (cases 3, 6, 7 and 11) a negative nitrogen balance on 60 Gm. of amino acids gave way to a positive balance when 90 to 120 Gm. was used. In still others (cases 1, 2, 5, 8 and 9) 60 Gm. was sufficient to produce at least a modest positive nitrogen balance. This lack of consistency in the requirements of amino acids for positive nitrogen balance would signify that in these cases it was a

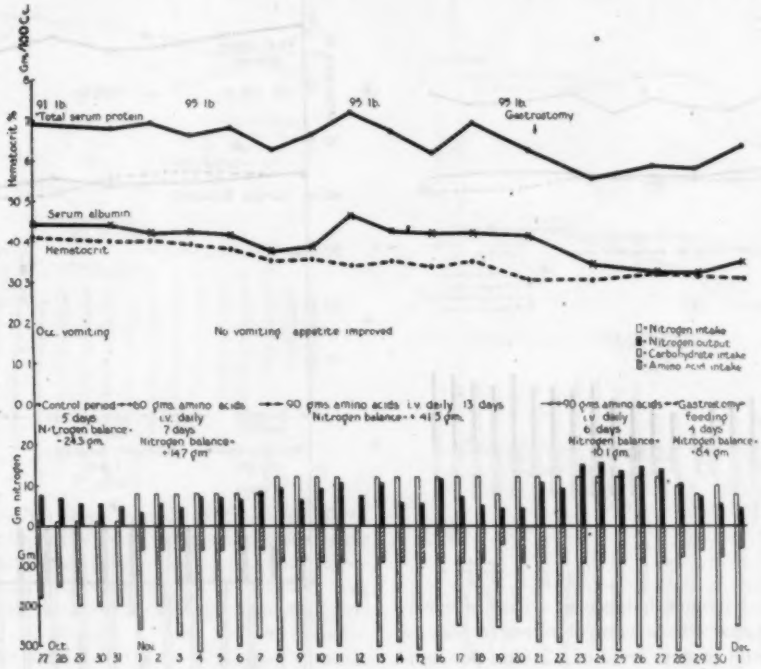

Fig. 5 (case 5).—Nitrogen balance study in a case of carcinoma of the esophagus with loss of 4.85 Gm. of nitrogen per day with a serum protein level of 6.9 Gm. per hundred cubic centimeters, serum albumin level of 4.4 Gm. and a hematocrit value of 41 per cent. When 60 Gm. of amino acids (Parenamine) was given intravenously per day, a positive nitrogen balance of 2.1 Gm. per day occurred, with a gain in weight of 4 pounds (1.8 Kg.). The serum proteins fell to 6.2 Gm. per hundred cubic centimeters, the serum albumin to 3.8 Gm. and the hematocrit value to 35 per cent. On 90 Gm. per day, a positive nitrogen balance of 3.2 Gm. per day resulted, with a restoration of serum albumin. The same quantity of amino acids postoperatively produced a negative nitrogen balance of 1.6 Gm. per day with a drop in serum protein and albumin, which is slight in comparison with usual nitrogen losses following surgical treatment. A positive nitrogen balance of 2.1 Gm. per day was also achieved when the amino acids were administered in gastrostomy feedings.

question not of possible insufficiency of one or more essential amino acids but of the special metabolic requirements of the individual patient. When the control excretion was moderate, there was usually no difficulty in obtaining a positive balance; when it was high, much larger quantities of amino acids were required, so large at times as to be impossible to administer by parenteral means. However, other special and indefinable factors operated in some cases. It was found, for example, difficult to produce positive nitrogen balance in the period immediately following operation on the gastrointestinal tract. This was found not only in this series but in another, as yet unreported, series of cases of gastrectomy for

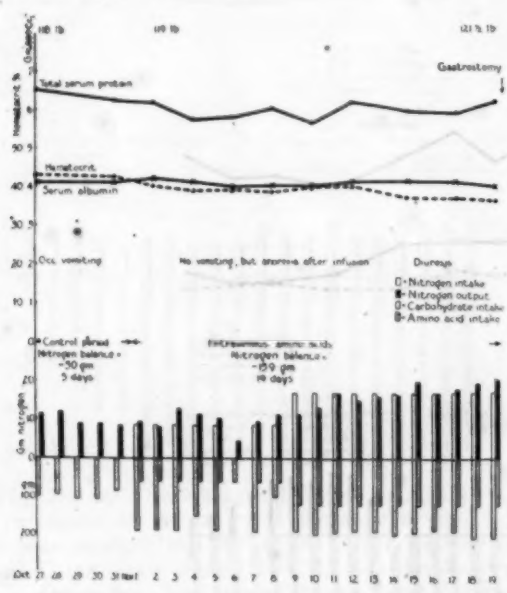

Fig. 6 (case 6).—Nitrogen balance in a case of carcinoma of the esophagus with a control nitrogen loss of 10 Gm. per day, serum protein level of 6.5 Gm. per hundred cubic centimeters, serum albumin level of 4.2 Gm. and hematocrit reading of 43 per cent. With 60 Gm. of amino acids (Cutter's) per day, a negative nitrogen balance of 2.3 Gm. per day resulted, with a drop in serum protein to 6.0 Gm. per hundred cubic centimeters, albumin to 4.0 Gm. and hematocrit value to 38.5 per cent. On 120 Gm. of amino acids per day (17 Gm. nitrogen), an over-all positive nitrogen balance of only 0.3 Gm. per day was achieved, which did not persist. The serum proteins were then 6.2 Gm. per hundred cubic centimeters; the serum albumin was 4.1 Gm., and the hematocrit value was 37 per cent.

peptic ulcer. Such a finding is in confirmation of that of Mulholland and associates.[16]

16. Mulholland, J. H.; Co Tui; Wright, A. M., and Vinci, V. J.: Nitrogen Metabolism, Caloric Intake and Weight Loss in Postoperative Convalescence: A Study of Eight Patients Undergoing Partial Gastrectomy for Duodenal Ulcers, Ann. Surg. **117**:512, 1943.

One factor which undoubtedly determined the amino acid requirement was the quantity of carbohydrate that could be given, just as it determined the amount of nitrogen excreted in the control periods. If the patient could take fluids by mouth, the wastage of amino acids as fuel was minimized. But in those cases of complete obstruction in which all nutrition had to be given parenterally, the limitations of carbohydrate administration produced corresponding limitations of amino acid utilization. This well known biochemical phenomenon, though reemphasized by Elman,[17] has frequently been lost sight of in the clinical utilization of amino acids.

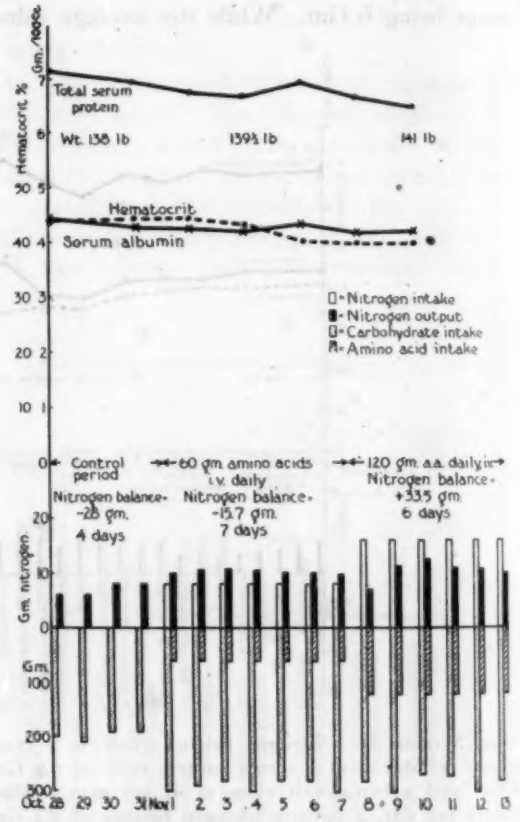

Fig. 7 (case 7).—Nitrogen balance study in the case of a patient who refused surgical treatment for carcinoma of the esophagus, with a control nitrogen loss of 7 Gm. per day, serum protein level of 7.1 Gm. per hundred cubic centimeters, albumin level of 4.4 Gm. and a hematocrit value of 45 per cent. With 60 Gm. of amino acids (Parenamine) given intravenously daily, a negative nitrogen balance of 2.2 Gm. per day resulted. On 120 Gm. of amino acids per day, a positive nitrogen balance of 5.6 Gm. per day was produced. The decline in serum proteins to 6.4 Gm. per hundred cubic centimeters and serum albumin to 4.1 Gm. is understandable, considering the drop in the hematocrit value to 39.5 per cent.

17. Elman, R.: Parenteral Fluids and Food in Gastro-Intestinal Disease, Bull. New York Acad. Med. **20**: 220, 1944.

The degree of clinical improvement was not always parallel to the gain in nitrogen. When there was no progressively deteriorating condition (case 1), gain in weight, cessation of nausea and vomiting, increased strength and sense of well-being were the accompaniments of positive nitrogen balance, but in the cases of rapidly metastasizing cancers (cases 8, 9 and 11) no

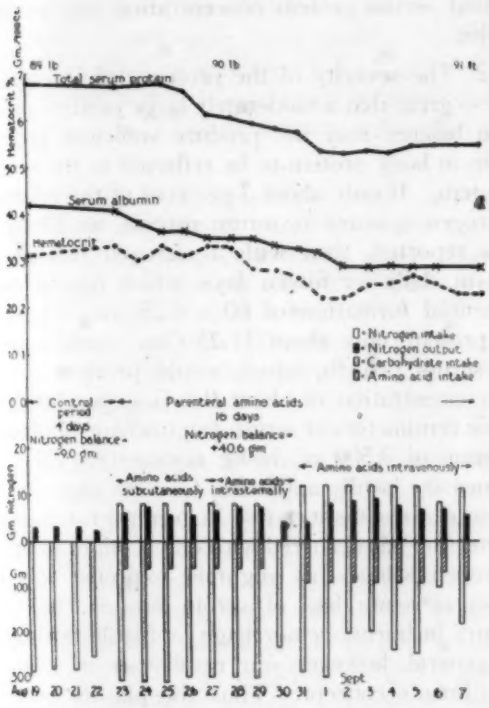

Fig. 8 (case 8).—Nitrogen balance study in a case of carcinoma of the esophagus in which amino acids were administered subcutaneously, intrasternally and intravenously. The control nitrogen loss was 2.25 Gm. per day, the serum protein level 6.8 Gm. per hundred cubic centimeters, the serum albumin 4.2 Gm. and the hematocrit reading 31 per cent. With 60 Gm. amino acids (Parenamine) injected subcutaneously per day, a positive nitrogen balance of 1.1 Gm. was observed. With 90 Gm. given intravenously daily (except for 60 Gm. on one day) a positive nitrogen balance of almost 4 Gm. per day was achieved. The decline in serum protein and albumin is greater than can be accounted for by the hemodilution produced.

such improvement was visible. The inexorable course of the disease was unaffected. Gain in weight occurred in most of the patients, whether the nitrogen balance was positive or negative. This gain was undoubtedly due chiefly to retention of water, for the minimal caloric requirements were seldom surpassed. Nevertheless, it was frequently associated with a sense of well-being, as if the rehydration were accompanied by a restoration of a more nearly normal water and electrolyte pattern, not only in the interstitial spaces but in the cells themselves.

The serum concentrations of total protein and albumin showed an irregular response to the gain in nitrogen. In some cases (cases 1, 2, 10 and 11) they rose with the positive nitrogen balance. In case 4, even though there was always a negative balance, a slight transitory rise in serum protein levels occurred. In 2 cases (cases 4 and 12) the initial and final serum protein levels remained unchanged, but the serum albumin level improved somewhat. On the other hand, in a larger number of cases (cases 3, 5, 6, 7, 8, 9, 13 and 14), even in the presence of positive nitrogen balance, not only was there no rise in serum protein concentrations but there were even de-

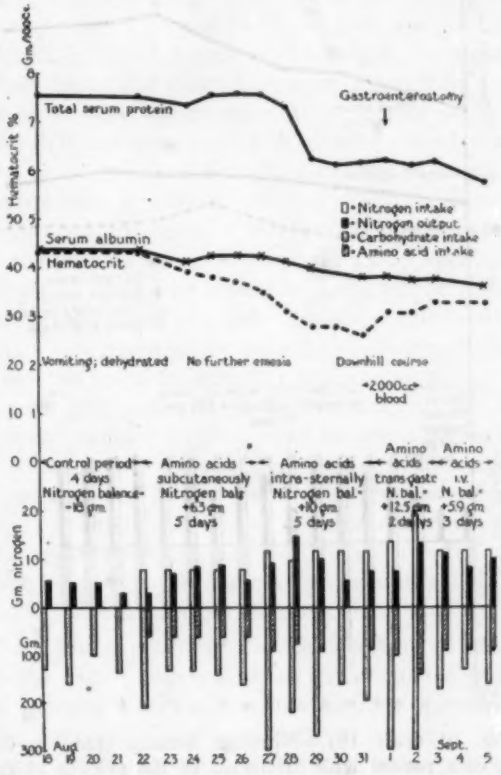

Fig. 9 (case 9).—Nitrogen balance study in a case of carcinoma of the stomach in which amino acids were given subcutaneously, intrasternally and intravenously. The nitrogen loss during the control period was 4.5 Gm. per day, the serum protein level 7.5 Gm. per hundred cubic centimeters, the serum albumin level 4.3 Gm. and the hematocrit value 43 per cent. Sixty grams of amino acid (Parenamine) injected subcutaneously produced a nitrogen balance of 1.25 Gm. per day. Ninety grams of amino acids (except 60 Gm. on one day) resulted in a positive nitrogen balance of 20 Gm. per day. A pronounced drop in the serum protein level could not be accounted for entirely by the hemodilution produced. Although a positive nitrogen balance was maintained by both transgastric and intravenous routes and despite the use of 2,000 cc. of blood, a downhill course could not be avoided, because of an extensive carcinomatous lesion.

clines, which in several cases were precipitous. The decline in serum proteins was usually greater than that of serum albumin. The reasons for this failure, apparent or real, of the serum protein and the albumin to respond to nitrogenous gain could not always be elicited, but the following factors are at least partly operative in these cases:

1. The gain in serum protein was masked by expansion of blood volume. This was indicated by the prevailing tendency for the hematocrit reading to drop during the period of study. Though a portion of this drop may be due to the progressive anemia caused by iron deficiency and the nature of the illness, the principal factor involved is expansion of a previously contracted plasma volume. Expansions of the order indicated by the changes in hematocrit readings in our cases[18] have been reported for such cases by Abbott and Mellors,[19] who used the Evans blue method for the determination of plasma volume. These authors demonstrated that a pronounced increase in the total circulating protein, which is equal to the concentration of protein per cubic centimeter times the number of cubic centimeters of total plasma volume, may occur in the presence of hemodilution, even though the actual serum protein concentration has actually fallen.

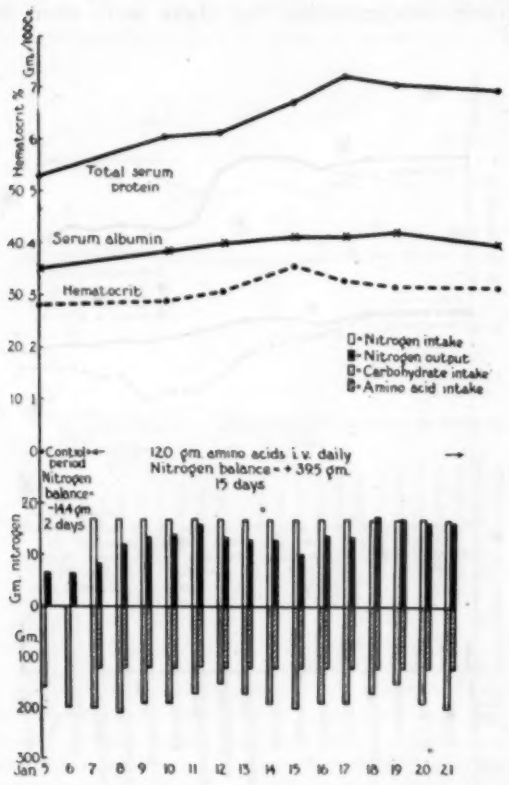
Hematocrit % Gm./100c.
Total serum protein
Serum albumin
Hematocrit
Nitrogen intake
Nitrogen output
Carbohydrate intake
Amino acid intake
Control period
Nitrogen balance = -144 gm. 2 days
120 gm. amino acids i.v. daily
Nitrogen balance = + 395 gm. 15 days
Gm. nitrogen
Gm.
Jan 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Fig. 10 (case 10).—Nitrogen balance study in the case of a patient with carcinoma of the pylorus of the stomach losing 7.2 Gm. of nitrogen per day with a serum protein level of 5.3 Gm. per hundred cubic centimeters, serum albumin of 3.5 Gm. and hematocrit reading of 28 per cent. When 120 Gm. of amino acids (Cutter's) was given intravenously daily, the patient achieved a positive nitrogen balance of 2.6 Gm. per day with a rise in serum proteins to 7.0 Gm. per hundred cubic centimeters, of serum albumin to 4.0 Gm. and of the hematocrit value to 32 per cent. Note, however, that the nitrogen intake and output rapidly achieved a state of equilibrium.

2. The severity of the protein deficiency may be so great that a moderately large positive nitrogen balance may not produce sufficient general gain in body protein to be reflected in the serum protein. If only about 3 per cent of the retained nitrogen appears as serum protein, as Elman[20] has reported, then with a nitrogen balance of 4 Gm. daily for fifteen days, which represents a potential formation of 60×6.25, or 375, Gm. of protein, only about 11.25 Gm. would appear as serum protein, which would produce a rise in concentration of about 0.3 Gm. per hundred cubic centimeters of serum (an unchanged plasma volume of 3,500 cc. being assumed). Elman's values are hardly applicable to every case, for in some cases a distinct rise in serum protein concentration has occurred with only a slight positive nitrogen balance, as might be expected only in cases of acute loss of serum protein, such as occurs in burns, hemorrhage or fistula drainage. In general, however, our results are in support of Elman's concept. Thus the plasma protein concentration may be regarded as similar to a glass gage on the side of a water tank; a small fall or rise in the gage represents a large loss or gain in the tank proper.

18. The formula for the determination of the percentile increase in plasma volume with decrease in hematocrit, assuming no change in the red cell volume, is as follows:

$$\frac{H_o}{(100\text{-}H_o) + \frac{X\ (100\text{-}H_o)}{100}} = \frac{H_1}{100\text{-}H_1}$$

where H_o is the initial hematocrit, H_1 the final hematocrit and X the percentile increase in plasma volume. Solving for X,

$$X = \frac{10{,}000\ (H_o - H_1)}{H_1\ (100\text{-}H_o)}$$

For example, if an initial hematocrit of 39 per cent becomes 34 on hemodilution, then the percentile increase in plasma volume is

$$\frac{10{,}000\ (39\text{-}34)}{(34)\ (61)} = 24.1\ \%$$

19. Abbott, W. E., and Mellors, R. C.: Total Circulating Plasma Proteins in Surgical Patients with Dehydration and Malnutrition, Arch. Surg. **46**:277 (Feb.) 1943.

20. Elman, R., and Lischer, C.: The Occurrence and Correction of Hypoproteinemia (Hypoalbuminemia) in Surgical Patients, Internat. Abstr. Surg. **76**:503, 1943; in Surg., Gynec. & Obst., June 1943.

The severity of the protein deficiency in a group of patients such as those studied here can be determined in another way. The average loss of weight was 16 Kg. It is of course impossible to determine the distribution of that loss in terms of water, protein and fat. But if one assumes that such patients show a relationship of nitrogen to loss of weight corresponding to that found by Lusk [21] in the study of undernourished persons—that is, 30 Gm. of nitrogen for each kilogram of body weight lost—then these patients have lost about 480 Gm. of nitrogen. A daily positive nitrogen balance of 4 Gm. would be required for one hundred and twenty days to restore the lost protein.

3. The gain in nitrogen may be used up in the growth of metastases. In the patients with rapidly metastasizing carcinomas, positive nitrogen balance was not difficult to achieve. Their urinary nitrogen excretion was small and that of the feces negligible. There was no elevation of the blood nonprotein nitrogen. Yet these patients, in spite of good positive nitrogen balances, not only showed no clinical improvement but manifested a precipitous drop in serum protein too great to be accounted for by the simultaneous hemodilution. Since at autopsy extensive formation of new tissue as metastases was observed, it is possible that the increase in the growth of the neoplasm utilizes the available nitrogen at the expense of the plasma proteins, even in the face of a positive nitrogen balance. Such a phenomenon is consistent with the recent observations of White and Belkin [22] that tumor transplants in rats grow rapidly in spite of negative nitrogen balances associated with a low protein diet, apparently at the expense of the tissues of the host.

4. The albumin-making mechanisms, which are believed to be found chiefly in the liver, may be damaged enough to prevent a rise in serum albumin. To this phenomenon has generally been attributed the fall of serum albumin in cirrhosis of the liver, though it should be recognized that the continued production of serum protein in cirrhosis in spite of the repeated removal of large quantities by paracentesis would indicate, on the contrary, a stimulation of albumin production similar to that seen in the plasmapheresis experiment in dogs by Whipple and his co-workers.[23] However, low serum protein concentrations are not infrequently encountered in cases of cirrhosis without ascites, and it may be that cases of carcinoma with extensive metastases to the liver are similarly involved. Furthermore, there is the possibility that severe protein deficiency itself is capable of undermining the ability of the liver to manufacture albumin, even when furnished with an adequate supply of amino acids. If such were the case, a rise in serum protein level might not occur until the liver itself has been restored.

Available data on the blood concentrations and urinary excretions of amino acid nitrogen, phosphate, sulfate, urea and creatinine have been omitted as not being pertinent to the main thesis of this paper. It can be stated that the morning plasma levels of amino acid nitrogen during the whole treatment ranged between 3 and 8 mg. per hundred cubic centimeters, as in normal persons. The daily urinary excretion of amino acid nitrogen ranged from 0.2 to 0.6 Gm. and thus represented only a small portion of the administered amino acid nitrogen. The chief portion appeared in the urine as urea. Phosphate was found practically to disappear from the urine as the parenteral regimen progressed. Since very little phosphate was given to the patients, its disappearance from the urine indicated a purposeful retention. Serum phosphate levels were usually in the low normal range. Sulfate was excreted at nearly constant rates, the nitrogen-sulfur ratios ranging from 1 : 14 to 1 : 20, which is of the same order as in normal feeding. Creatinine excretion was remarkably variable and for the most part lower than normal. All these observations are to be the subjects of further investigations.

In clinical practice, it is not necessary to adhere to the use of amino acids as the exclusive source of protein, as was done in this investigation for the purpose of nitrogen balance studies. Much more satisfactory responses can be expected if parenterally injected amino acids are supplemented with dietary protein whenever the patients are capable of taking food by mouth. Furthermore, in view of the anemia of these patients, massive injections of whole blood are indicated. Transfusions of 2,000 cc. have been found by us to be superior to injections of plasma or amino acids for producing an immediate elevation of serum protein concentrations. Thus the combined use of protein, blood transfusions, carbohydrate intake of 300 Gm. or more and paren-

21. Lusk, G.: The Physiological Effect of Undernutrition, Physiol. Rev. **1**:523, 1921.

22. White, F. R., and Belkin, M.: Sources of Tumor Proteins: I. Effect of a Low-Nitrogen Diet on the Establishment and Growth of a Transplanted Tumor, J. Nat. Cancer Inst. **5**:261, 1945.

23. Whipple, G. H., and Madden, S. C.: Hemoglobin, Plasma Protein and Cell Protein—Their Interchange and Construction in Emergencies, Medicine **23**:215, 1944.

teral injections of amino acids offers the greatest possibilities for restoring tissue and serum proteins to normal levels.

SUMMARY AND CONCLUSIONS

Parenteral injections of amino acids were used as the only source of protein during a study of nitrogen balance in 14 cases of obstructing lesions of the esophagus or stomach. In 11 cases Parenamine (Stearns) was used and in 3 cases Cutter's amino acids.

Positive nitrogen balance was achieved in 13 of the 14 cases.

The quantity of amino acids required by parenteral injection for positive nitrogen balance usually varied between 60 and 90 Gm. per day. At times doses of 120 Gm. were more successful in producing larger positive balances.

The serum protein concentration rose during treatment in 4 cases, remained stationary in 2 and fell in 8. The serum albumin concentration rose in 6 cases and declined in 8.

The following factors may have been involved in the failure of the serum protein to rise in response to the attainment of positive nitrogen balance:

(*a*) Hemodilution, which occurred in most of the cases, masks an increase in serum protein.

(*b*) The severity of the protein deficiency in the type of cases studied here may be so severe as to require a much longer period of protein deficiency can be rectified. positive nitrogen balance before the entire

(*c*) Gain in nitrogen may be used up in the growth of metastases from carcinoma.

(*d*) The albumin-synthesizing mechanisms of the body may be interfered with by the presence of carcinoma with hepatic metastases or by a severe protein deficiency of the liver.

Therapy with parenteral injections of amino acid should be accompanied with an effort to meet the requirements of carbohydrate, minerals and vitamins. A minimal daily carbohydrate intake of 300 Gm. should be assured.

Therapy with parenteral injections of amino acid is only partly successful when the nitrogen losses are excessively high, since in such circumstances it is impossible to inject the required amounts of amino acids.

In clinical practice, two adjuvants to enhance the effects of therapy with parenteral injections of amino acid are recommended: (*a*) oral, intragastric or transgastric feedings of protein or amino acids and (*b*) transfusions of whole blood.

Miss Leah Gluck, A.B., made the nitrogen analyses, and Mrs. Betty Vallancey administered the amino acids and collected the specimens.